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<b>(54) Title:</b> TROPOELASTIN DERIVATIVES			
<b>(57) Abstract</b> <p>The invention relates to derivatives of tropoelastin and variants of those derivatives. The invention further provides expression products and hybrid molecules of the derivatives and variants of the invention. The invention further provides methods for the production of the derivatives, variants, expression products and hybrid molecules. Further provided are formulations, cross-linked structures and implants comprising the derivatives, variants, expression products and hybrid molecules of the invention. Further provided are uses of the derivatives, variants, expression products and hybrid molecules of the invention.</p>			

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## TROPOELASTIN DERIVATIVES

### TECHNICAL FIELD

The present invention relates to derivatives of human  
5 tropoelastin and variants thereof, to genetic constructs  
encoding the amino acid sequences of the derivatives and  
variants and to uses of the derivatives and variants. In  
particular, the derivatives of the present invention have  
elastin-like properties or macro-molecular binding  
10 properties.

### BACKGROUND ART

There are various forms of tropoelastin that  
typically appear to consist of two types of alternating  
15 domains: those rich in hydrophobic amino acids  
(responsible for the elastic properties) and those rich in  
lysine residues (responsible for cross-link formation).  
Hydrophobic and cross-linking domains are encoded in  
separate exons (Indik et al 1987).

20 The 26 A region of human tropoelastin is unique  
amongst tropoelastin domains in that, due to the absence  
of lysine, this region does not participate in elastin  
cross-link formation. Furthermore, this region is a  
serine-rich domain and lacks hydrophobic stretches,  
25 indicating that it is unlikely to contribute to the  
elasticity of tropoelastin. There is otherwise limited  
information on the structure and functional relationships  
of the 26 A region (Bedell-Hogan et al., 1993).

The gene for tropoelastin is believed to be present  
30 as a single copy in the mammalian genome, and is expressed  
in the form of multiple transcripts, distinguished by  
alternative splicing of the pre-mRNA (Indik et al, 1990;  
Oliver et al, 1987). Modest expression of a natural human  
tropoelastin sequence has been achieved by Indik et al  
35 (1990) using cDNA, providing free polypeptide which  
unfortunately was unstable.

Expression of substantial amounts of human  
tropoelastin using synthetic polynucleotides is reported

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in WO94/14958. In particular, a construct, SHEL, providing substantial amounts of full length human tropoelastin is described.

5

#### DESCRIPTION OF THE INVENTION

In the specification and claims, "derivatives of human tropoelastin" or "tropoelastin derivatives" means novel peptides, polypeptides or proteins which contain amino acid sequences derived from the native amino acid sequences of human tropoelastin molecules. The amino acid sequences of the derivatives of human tropoelastin may be derived from any of the amino acid sequences of the isoforms of human tropoelastin. Derivatives of human tropoelastin are distinguished from human tropoelastin molecules in that the amino acid sequences of derivatives are altered with respect to native tropoelastin sequences by substitution, addition or deletion of residues, or a combination of these alterations, in derivative amino acid sequences.

20 In a first aspect, the present invention provides derivatives of human tropoelastin which have elastin-like properties. Elastin-like properties are a combination of elastic properties, including the phenomenon of recoil following molecular distention under appropriate conditions, and the ability to be cross-linked to other elastin molecules and/or other elastin-like molecules.

25 In a second aspect, the present invention provides derivatives of human tropoelastin which have macro-molecular binding properties including the ability to bind glycosaminoglycans.

30 In a third aspect, the present invention provides derivatives of human tropoelastin which have elastin-like properties and macro-molecular binding properties.

35 The present invention further provides amino acid sequence variants of the derivatives of the invention. In the specification and claims "variants" means amino acid sequences which retain the properties of the corresponding derivative of human tropoelastin, for example, elastin-

like properties or macro-molecular binding properties, or a combination of elastin-like properties and macro-molecular binding properties, and have an amino acid sequence which is homologous with the amino acid sequence of the corresponding derivative. For the purposes of this description, "homology" between the amino acid sequence of a particular derivative of human tropoelastin and another amino acid sequence connotes a likeness short of identity, indicative of a derivation of one sequence from the other. In particular, an amino acid sequence is homologous to a derivative of human tropoelastin if the alignment of that amino acid sequence with the sequence of the derivative of human tropoelastin reveals a similarity of about 65% over any 20 amino acid stretch or over any repetitive element of the molecules shorter than 20 amino acids in length. Such a sequence comparison can be performed via known algorithms, such as that of Lipman and Pearson (1985). Similarity is observed between amino acids where those amino acids have a side chain which confers a similar chemical property in the same chemical environment. For example, threonine and serine are similar amino acids; aspartic acid and glutamic acid are similar amino acids; valine, leucine and isoleucine are similar amino acids etc. Thus, an amino acid sequence may be considered homologous with the amino acid sequence of a human tropoelastin derivative because the alignment of those sequences reveals a similarity of 65%, although at each amino acid position in the aligned sequences, none of the residues are identical.

Inasmuch as the present invention provides derivatives of human tropoelastin and amino acid sequence variants of those derivatives, the invention thus extends to amino acid sequence variants incorporating amino acid sequences of non-human tropoelastins. Amino acid sequence variants which are non-human tropoelastin derivatives, or are based all, or in part, on non-human tropoelastin derivatives retain properties of the corresponding derivative of non-human tropoelastin, for example,

elastin-like properties or macro-molecular binding properties, or a combination of elastin-like properties and macro-molecular binding properties, and have an amino acid sequence which is homologous with the amino acid sequence of the corresponding human derivative. The variants of the invention also include variants of the non-human tropoelastin derivatives, or of derivatives based on the non-human tropoelastin derivatives.

"Homology" between the amino acid sequence of a particular derivative of non-human tropoelastin and another amino acid sequence connotes a likeness short of identity, indicative of a derivation of one sequence from the other. In particular, an amino acid sequence is homologous to a derivative of non-human tropoelastin if the alignment of that amino acid sequence with the sequence of the derivative of non-human tropoelastin reveals a similarity of about 65% over any 20 amino acid stretch or over any repetitive element of the molecules shorter than 20 amino acids in length. The skilled addressee will understand that species that are substantially phylogenetically related to humans express tropoelastin molecules which consist of amino acid sequences with homology to human tropoelastin amino acid sequences. Indeed, amino acid sequences of non-human tropoelastins have been determined, including the amino acid sequences of chick tropoelastin, bovine tropoelastin and rat tropoelastin (Bressan *et al.* 1987, Raju *et al.* 1987, Pierce *et al.* 1992) and over multiple regions, these are homologous with the human tropoelastin amino acid sequences. The skilled addressee will recognise therefore, that derivatives of human tropoelastin and amino acid sequence variants of those derivatives will necessarily encompass corresponding tropoelastin amino acid sequences from these and other non-human species.

The present invention provides a tropoelastin derivative comprising the amino acid sequence of SHEL $\delta$ modified (SEQ ID NO:5). The amino acid sequence of

SHELδmodified and the alignment of that amino acid sequence with the human tropoelastin sequence is shown in Figure 5.

The invention also provides an amino acid sequence  
5 variant of the derivative comprising the amino acid sequence of SHELδmodified.

The invention also provides a polynucleotide encoding a tropoelastin derivative comprising the amino acid sequence of SHELδmodified. The nucleotide sequence  
10 encoding SHELδmodified is shown in Figure 3 (SEQ ID NO: 4). Preferably the polynucleotide comprises the nucleotide sequence which corresponds to SHELδmodified shown in Figure 3.

The invention also provides a polynucleotide encoding  
15 an amino acid sequence variant of the derivative SHELδmodified.

The present invention further provides a synthetic polynucleotide encoding a tropoelastin derivative comprising the amino acid sequence of SHELδ26A (SEQ ID  
20 NO:3). A synthetic polynucleotide is a molecule which comprises a nucleotide sequence that contains silent mutations with respect to the corresponding native polynucleotide molecule. The silent mutations enhance the expression of the synthetic polynucleotide. The amino  
25 acid sequence of SHELδ26A and the alignment of that amino acid sequence with the human tropoelastin sequence is shown in Figure 2. The SHELδ26A derivative excludes the SHEL coding sequence corresponding to exon 26A. Preferably the synthetic polynucleotide comprises the  
30 sequence shown in Figure 1 (SEQ ID NO:1) from nucleotide position 1 to 1676 contiguous with nucleotide position 1775 to 2210.

The invention also provides a polynucleotide encoding an amino acid sequence variant of the derivative SHELδ26A.

35 The invention also provides an amino acid sequence

variant of the derivative comprising the amino acid sequence of SHEL826A.

The present inventor has, for the first time, shown that the region encoded by exon 26A (peptide 26A) of the tropoelastin gene binds glycosaminoglycans (GAGs) (Figure 6A and B). GAGs are macro-molecules particularly associated with the extracellular environment. These molecules play an important role in the architecture and mechanical properties of connective tissues and mediate interactions with and availability of other molecules.

Thus, the present invention provides a tropoelastin derivative comprising the amino acid sequence of peptide 26A. Peptide 26A has the amino acid sequence: GADEGVRRSLSPELREGDPSSSQHLPSTPSSPRV (SEQ ID NO: 12) or GADEGVRRSLSPELREGDPSSSQHLPSTPSSPRF (SEQ ID NO: 13).

The present invention also provides an amino acid sequence variant of the derivative comprising the amino acid sequence of peptide 26A.

The invention also provides a polynucleotide encoding a tropoelastin derivative comprising the amino acid sequence of peptide 26A. Preferably the polynucleotide comprises the nucleotide sequence shown in Figure 1 (SEQ ID NO: 1) from nucleotide position 1687 to 1778. Preferably the 3' terminal codon is GTT (which encodes V) or TTT (which encodes F).

The invention also provides a polynucleotide encoding an amino acid sequence variant of the derivative comprising the amino acid sequence of peptide 26A.

In appreciating the GAG binding property of peptide 26A, the present inventor envisages the generation of novel subsets of hybrid molecules, comprising biological polymers which are linked to peptide 26A, wherein the peptide 26A imparts GAG binding activity to the polymer. In particular, the present inventor has recognised that the deletion or insertion of the peptide 26A amino acid sequence, or a variant of that amino acid sequence will alter GAG binding activity. Thus, the present invention relates to tropoelastin derivatives in which full length



or partial length tropoelastin molecules have been modified by the addition of one or more exon 26A regions to enhance interactions with GAGs. Moreover, the invention relates to site directed modification of the amino acid sequence of peptide 26A so as to generate variants of the peptide 26A amino acid sequence which have altered affinity or altered specificity for GAGs. Tropoelastin derivatives or variants of the derivatives which contain altered GAG binding activity may be uncross-linked or cross-linked.

In another aspect, the invention provides a hybrid molecule. In the specification and claims, "hybrid molecule" means a molecule comprising a biological polymer which is linked to a tropoelastin derivative comprising the amino acid sequence of peptide 26A or an amino acid sequence variant of a derivative comprising the amino acid sequence of peptide 26A. Preferably the biological polymer is a protein. More preferably the protein is selected from the group consisting of growth factors, cytokines and antibodies. Alternatively the biological polymer is selected from the group consisting of lipids, sugars or nucleic acids.

In one embodiment, and where the biological polymer is a protein, the hybrid molecule is produced by recombinant DNA techniques, including for example the construction of a nucleotide sequence which encodes the biological polymer and the tropoelastin derivative comprising the amino acid sequence of peptide 26A, or the amino acid sequence variant of a derivative comprising the amino acid sequence of peptide 26 A, in a single open reading frame. Alternatively, the hybrid molecule may be produced synthetically by solid phase peptide synthesis, including, for example the methods of synthesis disclosed in Merrifield (1963) or Knorr et al. (1989). Examples of peptide synthesis also include the synthesis methods used by peptide synthesisers of Perkin Elmer/Applied Biosystems, CA, US.

In another aspect, the invention provides a

polynucleotide sequence encoding a hybrid molecule of the invention.

In another aspect, the invention provides a hybrid molecule which comprises a synthetic polymer which is  
5 linked in a tropoelastin derivative comprising the amino acid sequence of peptide 26A, or an amino acid sequence variant of the derivative comprising the amino acid sequence of peptide 26A.

The invention further provides a method of imparting  
10 or enhancing GAG binding activity to a biological polymer comprising the step of linking a tropoelastin derivative comprising the amino acid sequence of peptide 26A, or an amino acid sequence variant of peptide 26A with the biological polymer. Preferably the biological polymer is  
15 a protein.

The invention further provides a method of deleting or reducing GAG binding activity from a biological polymer comprising the step of deleting a tropoelastin derivative comprising the amino acid sequence of peptide 26A, or an  
20 amino acid sequence variant of peptide 26A from the biological polymer. Preferably the biological polymer is a protein.

The present invention also provides a tropoelastin derivative comprising the amino acid sequence of  
25 SHELgamma. SHELgamma has the amino acid sequence:  
SAMGALVGLGVPGLVGAGVPGFGAGADEGVRRSLSPELREGDPSSSQHLPSTPSSPR  
VPGALAAAKAAKYGAAPGVGLGGLGALGGVGIPGGVVGAGPAAAAAAKAAKAAQFG  
LVGAAGLGGGLGVGGLGVPGVGGLGGIPPAKAAKYGAAGLGGVLGGAGQFPLGGVA  
ARPGFGLSPIFPGGACLGKACGRKRK (SEQ ID NO: 9).

30 The invention also provides an amino acid sequence variant of the derivative comprising the amino acid sequence of SHELgamma.

The invention also provides a polynucleotide encoding a tropoelastin derivative, the derivative comprising the  
35 amino acid sequence of SHELgamma. The nucleotide sequence of the polynucleotide SHELgamma (SEQ ID NO: 8) is shown in Figure 8. In this nucleotide sequence, the first 9 codons from nucleotide position 948 to 974 are derived

from the glutathione S-transferase (GST) fusion nucleotide sequence. Preferably the polynucleotide comprises the nucleotide sequence shown in Figure 8. More preferably the polynucleotide comprises the nucleotide sequence shown in Figure 8 from nucleotide sequence position 975 to 1547.

The invention also provides a polynucleotide encoding an amino acid sequence variant of the derivative comprising the amino acid sequence of SHELgamma.

The present invention also provides a polynucleotide encoding a tropoelastin derivative, the derivative comprising the amino acid sequence of SHELgamma excluding exon 26A. The nucleotide sequence of the polynucleotide SHELgamma excluding exon 26A (SEQ ID NO: 6) is shown in Figure 7. In this nucleotide sequence, the first 5 codons from nucleotide position 948 to 962 are derived from the GST nucleotide sequence. SHELgamma excluding exon 26A has the following amino acid sequence:

VPGALAAAKAAKYGA AVPGVLGGLGALGGVGIPGGVVGAGPAAAAAAKAAAKAAQFG  
LVGAAGLGGLGVGGLGVPGVGGLGGIPPAKAAKYGAAGLGGVLGGAGQFPLGGVA  
ARPGFGLSPIFPGGACLGKACGRKRK (SEQ ID NO: 7).

Preferably the polynucleotide comprises the nucleotide sequence shown in SEQ ID NO: 6. More preferably the polynucleotide comprises the nucleotide sequence shown in SEQ ID NO: 6 from nucleotide sequence position 15 to 441.

The invention also provides a polynucleotide encoding an amino acid sequence variant of the derivative comprising the amino acid sequence of SHELgamma excluding exon 26A.

The invention also provides a tropoelastin derivative comprising the amino acid sequence of SHELgamma excluding exon 26A.

The invention also provides an amino acid sequence variant of the derivative comprising SHELgamma excluding exon 26A.

The derivatives of the invention based on SHELgamma can also be produced by *in vitro* biochemical cleavage of tropoelastin products such as SHEL, so as to release a carboxy-terminal fragment. The carboxy-terminal fragment

may be purified by reverse phase HPLC.

The present invention also provides a tropoelastin derivative comprising the amino acid sequence of SHEL31-36. SHEL31-36 has the following amino acid sequence:

5 GIPPAAAAKAAKYGAAGLGGVLGGAGQFPLGGVAARPGFGLSPIFPGGACLGKACG-RKRRK (SEQ ID NO: 10).

SHEL31-36 retains a crosslinking domain. As a consequence of its elastin-like properties, it is envisaged that this and related tropoelastin derivatives  
10 can be used to interfere with tropoelastin deposition and formation of unaltered elastic fibre.

The invention also provides an amino acid sequence variant of the derivative comprising the amino acid sequence of SHEL31-36.

15 The invention also provides a polynucleotide encoding a tropoelastin derivative, the derivative comprising the amino acid sequence of SHEL31-36. Preferably the polynucleotide comprises the nucleotide sequence shown in Figure 1 (SEQ ID NO:1) from nucleotide position 2022 to  
20 2210.

The invention also provides a polynucleotide encoding an amino acid variant of the derivative comprising the amino acid sequence of SHEL31-36.

The present invention also provides a tropoelastin  
25 derivative, comprising the amino acid sequence of SHEL32-36. SHEL32-36 has the following amino acid sequence: GAAGLGGVLGGAGQFPLGGVAARPGFGLSPIFPGGACLGKACGRKRRK (SEQ ID NO: 11).

The invention also provides an amino acid sequence  
30 variant of the derivative comprising the amino acid sequence of SHEL32-36.

The invention also provides a polynucleotide encoding a tropoelastin derivative, the derivative comprising the amino acid sequence of SHEL32-36. Preferably the  
35 polynucleotide comprises the nucleotide sequence shown in Figure 1 (SEQ ID NO: 1) from nucleotide position 2061 to 2210.

The present invention also provides a polynucleotide

encoding an amino acid sequence variant of the derivative comprising the amino acid sequence of SHEL32-36.

As a consequence of its elastin-like properties, it is envisaged that SHEL32-36 and related tropoelastin derivatives can be used to interfere with tropoelastin deposition and formation of an unaltered elastic fibre.

The present invention also provides a tropoelastin derivative, comprising the amino acid sequence of SHEL26-36. SHEL26-36 has the following amino acid sequence:

10 AAAGLGAGIPGLGVGVGPGLGVGAGVPGLGVGAGVPGFGAGADEGVRRSLSPELREGD  
PSSSQHLPSTPSSPRVPGALAAAKAAKYGAAVPGVLGGLGALGGVGIPGGVVGAGPAAA  
AAAAKAAKAAQFGLVGAAGLGGLGVGGLGVPGVGGGIPPAKAAKYGAAGLGGLV  
LGGAGQFPLGGVAARPGFGLSPIFPGGACLKGACGRKRK (SEQ ID NO: 14)

The invention also provides an amino acid sequence variant of the derivative comprising the amino acid sequence of SHEL26-36.

The invention also provides a polynucleotide encoding a tropoelastin derivative, the derivative comprising the amino acid sequence of SHEL26-36. Preferably the polynucleotide comprises the nucleotide sequence shown in Figure 1 from nucleotide position 1554-2210.

The present invention also provides a tropoelastin derivative, comprising the amino acid sequence of SHEL26-36 excluding exon 26A. SHEL26-36 excluding exon 26A has the following amino acid sequence:

25 AAAGLGAGIPGLGVGVGPGLGVGAGVPGLGVGAGVPGFGAVPGALAAAKAAKYGAAVP  
GVLGGLGALGGVGIPGGVVGAGPAAAAAKAAKAAQFGLVGAAGLGGLGVGGLGVPG  
VGGLGGIPPAKAAKYGAAGLGGLVGGAGQFPLGGVAARPGFGLSPIFPGGACLKGA  
CGRKRK (SEQ ID NO: 15)

The invention also provides an amino acid sequence variant of the derivative comprising the amino acid sequence of SHEL26-36 excluding exon 26A.

The invention also provides a polynucleotide encoding a tropoelastin derivative, the derivative comprising the amino acid sequence of SHEL26-36 excluding exon 26A. Preferably the polynucleotide comprises the nucleotide sequence shown in Figure 1 from nucleotide position 1554

to 1676 contiguous with 1776 to 2210.

The present invention also provides a polynucleotide encoding an amino acid sequence variant of the derivative comprising the amino acid sequence of SHEL26-36.

5 In another aspect the present invention provides a formulation comprising a tropoelastin derivative, a variant of the derivative or a hybrid molecule of the invention, together with a carrier or diluent.

10 Formulations of the derivatives, variants or hybrid molecules of the invention can be prepared in accordance with standard techniques appropriate to the field in which they are to be used.

The polynucleotides and synthetic polynucleotides of the invention can be provided in association with other  
15 polynucleotide sequences including 5' and 3' untranslated sequences, and 5' upstream and 3' downstream transcriptional regulatory sequences. The polynucleotides and synthetic polynucleotides may be provided as a recombinant DNA molecule including plasmid DNA.

20 The polynucleotides and synthetic polynucleotides of the invention can be prepared using the techniques of chemical synthesis or recombinant DNA technology, or by a combination of both techniques.

In a further aspect the invention provides a vector  
25 comprising a polynucleotide or synthetic polynucleotide encoding a tropoelastin derivative, a variant of the derivative or a hybrid molecule of the invention.

Vectors useful in this invention include plasmids, phages and phagemids. The polynucleotides and synthetic  
30 polynucleotides of the present invention can also be used in integrative expression systems or lytic or comparable expression systems.

Suitable vectors will generally contain origins of replication and control sequences which are derived from  
35 species compatible with the intended expression host. Typically these vectors include a promoter located upstream from the polynucleotide, together with a ribosome binding site if intended for prokaryotic expression, and a

phenotypic selection gene such as one conferring antibiotic resistance or supplying an auxotrophic requirement. For production vectors, vectors which provide for enhanced stability through partitioning may be chosen. Where integrative vectors are used it is not necessary for the vector to have an origin of replication. Lytic and other comparable expression systems do not need to have those functions required for maintenance of vectors in hosts.

For *E. coli* typical vectors include pBR322, pBluescript II SK<sup>+</sup>, pGEX-2T, pTrc99A, pET series vectors, particularly pET3d, (Studier et al., 1990) and derivatives of these vectors. Derivatives include those plasmids with a modified protease recognition sequence to facilitate purification of a protein domain.

In another aspect the invention provides a cell capable of expressing a polynucleotide or a synthetic polynucleotide which encodes a derivative or variant of the invention, or a polynucleotide which encodes a hybrid molecule of the invention.

A preferred expression system is an *E. coli* expression system. However, the invention includes within its scope the use of other hosts capable of expressing protein from the polynucleotides designed for use in *E. coli*. The invention also includes the use of polynucleotides and synthetic polynucleotides suitable for use in other expression systems such as other microbial expression systems. These other expression systems include yeast, and bacterial expression systems, insect cell expression systems, and expression systems involving other eukaryotic cell lines or whole organisms.

Examples of *E. coli* hosts include *E. coli* B strain derivatives (Studier et al, 1990), and K-strain derivatives such as NM522 (Gough and Murray, 1983) and XL1-Blue (Bullock et al, 1987).

In a further aspect the present invention provides an expression product. In the specification and claims, "expression product" means a derivative or variant of the

invention expressed by a cell containing a polynucleotide or a synthetic polynucleotide encoding a derivative or variant of the invention.

5 The expression products of the invention may be fused expression products which include all or part of a protein encoded by the vector in peptide linkage with the derivative or variant. They may also include, for example, an N-terminal methionine or other additional residues which do not permanently impair the elastin-like, 10 or macro-molecular binding properties of the product.

Typically the fusion is to the N-terminus of the expression product. An example of a suitable protein is to the C-terminus of glutathione *S*-transferase. The fused protein sequence may be chosen in order to cause the 15 expression product to be secreted or expressed as a cell surface protein to simplify purification or expressed as a cytoplasmic protein.

The expressed fusion products may subsequently be treated to remove the fused protein sequences to provide 20 free tropoelastin derivative or variant. Treatment is typically through protease treatment or, in the case of secretion, removal is effected by endogenous host secretion machinery. An example of this is secretion by yeasts.

25 Non-fused systems include the introduction of or use of a pre-existing methionine codon. An example of this is the use of pET3a or pET3d in *E. coli*.

In another aspect the invention provides a polynucleotide encoding an expression product of the 30 invention.

In another aspect the present invention provides a formulation comprising an expression product of the invention together with a carrier or diluent. The 35 formulation of the expression product can be prepared in accordance with standard techniques appropriate to the field in which they are to be used.

According to a further aspect of the present invention there is provided a method for producing a



tropoelastin derivative or a variant of the derivative comprising providing a vector containing a polynucleotide or a synthetic polynucleotide encoding the derivative or variant; introducing the vector into a suitable host cell; 5 maintaining the cell in conditions suitable for expression of the polynucleotide or synthetic polynucleotide and isolating the derivative or variant of the invention. The method can be applied to the production of the expression products and hybrid molecules (in which the hybrid 10 molecules comprise the peptide 26A or a variant thereof and a further amino acid sequence) of the invention, by providing a vector containing a polynucleotide encoding an expression product or a hybrid molecule; introducing the vector into a suitable host cell; maintaining the cell in 15 conditions suitable for expression of the polynucleotide and isolating the expression product or hybrid molecule.

In one embodiment, the polynucleotide or synthetic polynucleotide encoding the derivative, variant, expression product or hybrid molecule of the invention is 20 expressed in a host cell which is maintained in culture *in vitro*.

Alternatively, the polynucleotide or synthetic polynucleotide encoding the derivative, variant, expression product or hybrid molecule of the invention is 25 expressed in a host cell which is maintained *in vivo*. Thus, in another embodiment, the polynucleotide or synthetic polynucleotide encoding the derivative, variant, expression product or hybrid molecule of the invention is expressed in a transgenic animal. Methods for the 30 generation of transgenic animals are known in the art. Exemplary methods are described in Slack et al. 1991 and Janne et al. 1992.

The tropoelastin derivatives, variants of the derivatives, and hybrid molecules (in which the hybrid 35 molecules comprise the peptide 26A or a variant thereof and a further amino acid sequence) of the invention may be produced by solid phase peptide synthesis, including, for example, the methods of synthesis disclosed in Merrifield

(1963) or Knorr et al (1989). Examples of peptide synthesis also include the synthesis methods used by peptide synthesizers of Perkin Elmer/Applied Biosystems, CA, US. As an alternative to cell synthesis from a polynucleotide or synthetic polynucleotide, the expression products of the invention may be produced by solid phase peptide synthesis.

In a further aspect the present invention provides an implant formed from at least one tropoelastin derivative and/or variant of the derivative of the invention. The implant may alternatively contain at least one expression product and/or at least one hybrid molecule of the invention.

The implants are formed into the required shape by cross-linking the tropoelastin derivative, variant of the derivative, expression product, or hybrid molecule of the invention, in a mould which conforms to the desired shape of the implant. Where the implant is required to be used in sheet form the tropoelastin derivative, variant of the derivative, expression product, or hybrid molecule of the invention can be cross-linked on a flat surface. Relevant methodologies are described in, for example, US Patent No. 4 474 851 and US Patent No. 5 250 516. The elastomeric materials may be exclusively prepared from one or more tropoelastin derivatives, variants of the derivative, expression products, or hybrid molecules of the invention or may be composites prepared from one or more of these constituents together with other materials.

The tropoelastin derivatives or variants of the derivatives can be cross-linked to form elastin or elastin-like material or can be cross-linked in conjunction with other biological or synthetic molecules to form a composite material.

Thus in another aspect the invention provides a cross-linked complex which comprises at least one tropoelastin derivative of the invention and/or at least one variant of a derivative of the invention. The cross-linked complexes may additionally contain at least one

expression product and/or at least one hybrid molecule of the invention, which may be cross-linked to the at least one tropoelastin derivative and/or variant of the derivative of the invention.

5       The cross-linking of the tropoelastin derivatives, variants of the derivatives, hybrid molecules and expression products of the invention can be achieved by chemical oxidation of lysine side chains using processes such as ruthenium tetroxide mediated oxidation and quinone  
10       mediated oxidation, or by using homobifunctional chemical cross-linking agents such as dithiobis (succinimidylpropionate), dimethyl adipimide or dimethyl pimelimide. Glutaraldehyde cross-linking is an important addition to this repertoire. Another alternative  
15       is the cross-linking of lysine and glutamic side chains.

      The tropoelastin derivatives, variants of the derivatives, hybrid molecules and expression products of the invention may also be enzymatically cross-linked by methods including lysyl oxidase mediated oxidation or may  
20       be cross-linked using gamma irradiation.

#### BRIEF DESCRIPTION OF THE DRAWINGS

      Figure 1: Nucleotide (SEQ ID NO: 1) and predicted amino acid (SEQ ID NO:2) sequences of synthetic human  
25       tropoelastin SHEL. The upper (numbered) nucleotide sequence represents the coding strand.

      Figure 2: Alignment of SHEL (SEQ ID NO:2) (upper line) and SHELδ26A (SEQ ID NO: 3) amino acid sequences.

      Figure 3: Nucleotide (SEQ ID NO: 4) and predicted  
30       amino acid (SEQ ID NO: 5) sequences of SHELδmodified.

      Figure 4: Alignment of SHELδmodified (SEQ ID NO: 4) (upper line) and SHEL (SEQ ID NO:1) nucleotide sequences.

      Figure 5: Alignment of SHELδmodified (SEQ ID NO: 5) (lower line) and SHEL (SEQ ID NO: 1) amino acid  
35       sequences.

      Figure 6A:       HPLC elution profile of GST-exon 26A fusion protein tropoelastin derivative loaded in from

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heparin sepharose. 6B: Binding of peptide 26A (SEQ ID NO: 12 and SEQ ID NO: 13) to glycosaminoglycans.

Figure 7: Nucleotide (SEQ ID NO: 6) and predicted amino acid (SEQ ID NO: 7) sequences of SHELgamma excluding  
5 exon 26A.

Figure 8: Nucleotide (SEQ ID NO: 8) and predicted amino acid (SEQ ID NO: 9) sequences of SHELgamma.

#### BEST METHOD OF PERFORMING THE INVENTION

10 The recombinant and synthetic procedures used for the synthesis of the derivatives, variants, expression products and hybrid molecules of the invention are described in standard texts such as Sambrook et al (1989).

Tropoelastin nucleotide sequences may be modified so  
15 as to provide derivatives, variants, expression products or hybrid molecules, by conventional site-directed or random mutagenesis. The sequences may also be modified by oligonucleotide-directed mutagenesis, which comprises the following steps:

- 20 1. synthesis of an oligonucleotide with a sequence that contains the desired nucleotide substitution (mutation);
2. hybridising the oligonucleotide to a template comprising a structural sequence encoding  
25 tropoelastin; and
3. using a DNA polymerase to extend the oligonucleotide as a primer.

Another approach which is particularly suited to situations where a synthetic polynucleotide encoding the  
30 tropoelastin derivative is prepared from oligonucleotide blocks bounded by restriction sites, is cassette mutagenesis where entire restriction fragments are replaced.

Purification of the derivatives, variants, expression  
35 products or hybrid molecules of the invention is performed using standard techniques including HPLC. The actual sequence of steps in the purification of a particular derivative, variant, expression product or hybrid molecule

is limited by the environment from which the molecule is to be purified. By way of example, reference is made to the purification scheme disclosed in W094/14958.

Formulations in accordance with the invention are  
5 formulated in accordance with standard techniques.

The amount of derivative, variant, expression product or hybrid molecule that may be combined with a carrier or diluent to produce a single dosage will vary depending on the situation in which the formulation is to be used and  
10 the particular mode of administration.

It will be understood also that specific doses for any particular host may be influenced by factors such as the age, sex, weight and general health of the host as well as the particular characteristics of the derivative,  
15 variant, expression product or hybrid molecule of the invention being used, and how it is administered.

Injectable preparations, for example, sterile injectable aqueous or oleagenous suspensions may be formulated according to the known art using suitable  
20 dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent. Among the acceptable vehicles or solvents that may be employed are  
25 water, Ringer's solution, alcohols and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition,  
30 fatty acids such as oleic acid and organic solvents find use in the preparation of injectables.

Routes of administration, dosages to be administered as well as frequency of administration are all factors which can be optimised using ordinary skill in the art.

35 In addition, the derivatives, variants, expression products and hybrid molecules of the invention may be prepared as topical preparations for instance as anti-wrinkle and hand lotions using standard techniques for the

preparation of such formulations. They may be prepared in aerosol form for, for instance, administration to a patient's lungs, or in the form of surgical implants, foods or industrial products by standard techniques.

5

#### SHEL

The preparation of SHEL is described in WO94/14958. It is directly expressed as a full length human protein with a calculated molecular weight of 64kDa. The full  
10 nucleotide sequence and corresponding amino acid sequence of SHEL is shown in Figure 1. The preparation of pSHELF is described in WO94/14958.

pSHELF differs from the natural coding sequence(s) in a number of ways. As described in WO94/14958, the  
15 untranslated regions present in the tropoelastin cDNA sequence were disregarded in designing the synthetic gene, and the nucleotides encoding the signal peptide were removed. Restriction endonuclease recognition sites were incorporated at regular intervals into the gene by  
20 typically altering only the third base of the relevant codons, thereby maintaining the primary sequence of the gene product. The facility for silent alteration of the coding sequence was also exploited to change the codon bias of the tropoelastin gene to that commonly found in highly  
25 expressed *E.coli* genes. [Genetics Computer Group (GCG) package version 7-UNIX using Codon Frequency and Gen Run Data: ecohigh-cod]. Two additional stop codons were added to the 3'-end, and an ATG start codon comprising a novel NcoI site was appended to the 5'-end. Bam HI cloning sites  
30 were engineered at both ends of the synthetic sequence. Since the gene contains no internal methionine residues, treatment of the newly-synthesized gene product (expressed directly or as a fusion with another gene) with cyanogen bromide would liberate a protein with the same or similar  
35 sequence as one form of natural tropoelastin comprising 731 amino acids. Other forms of processing are envisaged, which may generate tropoelastin species of the same or different lengths.

Two stop codons were added in order to allow the possible use of the construct in suppressor hosts, and also to avoid any potential depletion of termination (release) factors for translation.

5 As described in the following examples, the derivatives, pSHELF $\delta$ 26A, pSHELF $\delta$  modified, pSHELFgamma, pSHELF31-36, pSHELF32-36 and pSHELFgamma $\delta$ 26A were derived from the pSHELF nucleotide sequence. These particular derivatives, and indeed the derivatives, variants,  
10 expression products and hybrid molecules of the invention can equally be derived from a native human or non-human tropoelastin nucleotide sequence.

Example 1: Construction of pSHELF $\delta$ 26A and pSHELF $\delta$   
15 modified

Mutagenesis was used with pSHELF to remove DNA corresponding to exon 26A. The sequence of the mutagenic primer was:

5'CGG GTT TCG GTG CTG TTC CGG GCG CGC TGG 3'

20 This flanked either side of exon 26A by 15bp resulting in its precise deletion. A second selection primer, which mutates a unique restriction site to another restriction site is normally used in the protocol but was not in this case since deletion of exon 26A also resulted  
25 in the deletion of a unique restriction site, *Pml*I. The enzyme *Pml*I was used to treat the mutation reaction to linearise any unmutated parental plasmid and consequently to enrich for mutant plasmid. The reaction mixture was used to transform competent BMH17-18 *mutS* *E. coli*,  
30 defective in mismatch repair, by electroporation and the entire transformed culture was grown overnight in LB+ampicillin. Mixed plasmid DNA, containing both mutated and parental plasmids, was isolated from the culture and the plasmid DNA was digested with *Pml*I to linearise the  
35 parental plasmid. The plasmid DNA, now enriched for mutated plasmid, was used to transform *E. coli* HMS174 by electroporation and transformants selected on LB plates

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containing  $75\mu\text{gml}^{-1}$  ampicillin.

Colonies were grown overnight and plasmid mini-preparations performed. Constructs were screened using *Pml*I and those which were insensitive to digestion were further screened by *Kpn*I/*Pst*I double digestion. Candidate clones were sequenced to verify the sequence, named pSHELF $\delta$ modified.

Sequencing confirmed the region immediately surrounding the deletion was correct. *Pst*I and *Bss*HII restriction sites surrounding the correct region of pSHELF $\delta$ modified were used to remove the desired segment and re-insert it into the corresponding site of pSHELF. 6.5 $\mu\text{g}$  pSHELF and 7.5 $\mu\text{g}$  pSHELF $\delta$ modified were digested with *Bss*HII, precipitated and digested with *Pst*I. The appropriate three fragments were gel-purified and ligated. DNA was transformed into *E. coli* XL1-Blue and transformants selected on plates containing  $75\mu\text{gml}^{-1}$  ampicillin.

Plasmids were isolated by mini-preparations and screened using *Bgl*I digestion. A candidate clone was further analysed by restriction enzyme digestion and sequenced, and named pSHELF $\delta$ 26A.

#### Example 2: Synthesis of Exon 26A

The region of SHEL corresponding to exon 26A was amplified by PCR, with primers modified to introduce an in-frame *Bam*HI site upstream and a stop codon downstream at the 3' end. Two forms were generated: one terminating in valine (26AV) and the other terminating in phenylalanine (26AF). These forms are as follows:

GADEGVRRSLSPELREGDPSSSQHLPSTPSSPRV with properties:

Molecular weight = 3588.80

Residues = 34

Average Residue Weight = 105.553

Charge = -1

Isoelectric point = 5.71



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and

GADEGVRRSLSPELREGDPSSSQHLPSTPSSPRF

A 26A coding region was expressed as a glutathione S-transferase (GST) fusion protein.

5

Example 3: Glycosaminoglycan binding activity of Exon 26A

Ultrafiltration assay methodology was developed to examine and quantify interactions occurring *in vitro* between the 26A region and purified extracellular matrix glcosaminoglycans. GST26A fusion protein and tropoelastin were compared with GST and tropoelastin lacking exon 26A at physiologically relevant conditions of pH and ionic strength.

Experimental evidence supports the notion that peptide 26A (26AF and 26AV) binds GAGs. Immobilised heparin column binding shows that GST26A binds more tightly than does GST, and requires a higher sodium chloride concentration for elution (Figure 6B). Furthermore, GST26A fusion protein binds radioactive heparin with greater efficiencies than GST, and these can be compared with GAGs including chondroitin sulphates and keratin sulphates. An implication of this is that GAGs binding to tropoelastin can be adjusted based upon the content of 26A. Cross-linked tropoelastin would be expected to show differential binding to GAGs based on the relative amounts of SHEL vs. SHEL $\delta$ 26A.

In summary, these studies reveal that the 26A region is a functional glycosaminoglycan binding domain, which functions in intact tropoelastin. It is also active when isolated as a fusion entity yet displays no detectable structure in the absence of bound GAG. Furthermore, panel competition studies indicate a preference for those GAGs found in close association with the elastic fibre in the extracellular matrix.

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Example 4: Construction of pSHELgamma, pSHEL31-36, pSHEL32-36 and pSHELgammaδ26A

pSHELgamma is derived from the pSHELgamma construct disclosed in WO94/14958. pSHEL31-36, pSHEL32-36 and pSHELgammaδ26A were derived from pSHELgamma. pSHELgamma was modified by introducing an oligonucleotide linker at the KpnI site. This encoded a factor Xa cleavage site which could be utilised in subsequent constructs. PCR and site directed mutagenesis was then used to generate further, shorter forms which provided fusions with GST. Constructs were DNA sequenced for verification. Induced protein was isolated as GST-fusion proteins, which were subsequently bound to glutathione agarose. Protease cleavage was optional where fusion proteins were desired; otherwise the cleaved proteins and peptides were further purified by reverse phase HPLC.

INDUSTRIAL APPLICATION

The derivatives and expression products of the invention are of use in *inter alia* the medical, pharmaceutical, veterinary and cosmetic fields.

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## SEQUENCE LISTING

## (1) GENERAL INFORMATION:

(i) APPLICANT: WEISS, ANTHONY S  
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(ii) TITLE OF INVENTION: TROPOELASTIN DERIVATIVES

(iii) NUMBER OF SEQUENCES: 15

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(F) ZIP: 2060

(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk  
(B) COMPUTER: IBM PC compatible  
(C) OPERATING SYSTEM: PC-DOS/MS-DOS  
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30

(vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER: AU  
(B) FILING DATE:  
(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:

(A) APPLICATION NUMBER: AU PO8117  
(B) FILING DATE: 18-JUL-1997

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(2) INFORMATION FOR SEQ ID NO:1:

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## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2210 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: YES

(iv) ANTI-SENSE: NO

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

GATCCATGGG TGGCGTCCG GGTGCTATCC CGGGTGGCGT TCCGGGTGGT GTATTCTACC	60
CAGGCGCGGG TCTGGGTGCA CTGGGCGGTG GTGCGCTGGG CCCGGGTGGT AAACCGCTGA	120
AACCGGTTCC AGGCGGTCTG GCAGGTGCTG GTCTGGGTGC AGGTCTGGGC GCGTTCCCGG	180
CGGTTACCTT CCCGGGTGCT CTGGTTCCGG GTGGCGTTGC AGACGCAGCT GCTGCGTACA	240
AAGCGGCAAA GGCAGGTGCG GGTCTGGGCG GGGTACCAGG TGTGGCGGT CTGGGTGTAT	300
CTGCTGGCGC AGTTGTTCCG CAGCCGGGTG CAGGTGTAAA ACCGGGCAAA GTTCCAGGTG	360
TTGGTCTGCC GGGCGTATAC CCGGGTGGTG TTCTGCCGGG CGCGCGTTTC CCAGGTGTTG	420
GTGTACTGCC GGGCGTTCG ACCGGTGCAG GTGTTAAACC GAAGGCACCA GGTGTAGGCG	480
GCGCGTTCGC GGGTATCCCG GGTGTTGGCC CGTTCGGTGG TCCGCAGCCA GGC GTTCCGC	540
TGGGTTACCC GATCAAAGCG CCGAAGCTTC CAGGTGGCTA CCGTCTGCCG TACACCACCG	600
GTAAACTGCC GTACGGCTAC GGTCCGGGTG GCGTAGCAGG TGCTGCGGGT AAAGCAGGCT	660
ACCCAACCGG TACTGGTGTT GGTCCGCAGG CTGCTGCGGC AGCTGCGGCG AAGGCAGCAG	720
CAAAATTCGG CGCGGGTGCA GCGGGTGTTT TGCCGGGCGT AGGTGGTGCT GGC GTTCCGG	780
GTGTTCCAGG TCGATCCCG GGCATCGGTG GTATCGCAGG CGTAGGTACT CCGGCGGCCG	840

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CTGCGGCTGC GGCAGCTGCG GCGAAAGCAG CTAATACGG TGCGGCAGCA GGCCTGGTTC	900
CGGGTGGTCC AGGCTTCGGT CCGGGTGTG TAGGCGTTCC GGGTGTGGT GTTCCGGGCG	960
TAGGTGTTCC AGGTGCGGGC ATCCCGGTTG TACCGGGTGC AGGTATCCCG GGCCTGCGG	1020
TTCCAGGTGT TGTATCCCCG GAAGCGGCAG CTAAGGCTGC TGCGAAAGCT GCGAAATACG	1080
GAGCTCGTCC GGGCGTTGGT GTTGGTGGCA TCCCGACCTA CGGTGTAGGT GCAGGCGGTT	1140
TCCAGGTTT CCGCGTTGGT GTTGGTGGCA TCCCGGGTGT AGCTGGTGTT CCGTCTGTTG	1200
GTGGCGTACC GGGTGTGGT GGCCTCCAG GTGTAGGTAT CTCCCGGAA GCGCAGGCAG	1260
CTGCGGCAGC TAAAGCAGCG AAGTACGGCG TTGGTACTCC GGCAGGCAGCA GCTGCTAAAG	1320
CAGCGGCTAA AGCAGCGCAG TTCGGACTAG TTCCGGGCGT AGGTGTTGCG CCAGGTGTTG	1380
GCGTAGCACC GGGTGTGGT GTTGCTCCGG GCGTAGGTCT GGCACCGGGT GTTGGCGTTG	1440
CACCAGGTGT AGGTGTTGCG CCGGGCGTTG GTGTAGCACC GGTATCGGT CCGGGTGGCG	1500
TTGCGGCTGC TGCGAAATCT GCTGCGAAGG TTGCTGCGAA AGCGCAGCTG CGTGCAGCAG	1560
CTGGTCTGGG TGCGGGCATC CCAGGTCTGG GTGTAGGTGT TGGTGTTCG GGCCTGGGTG	1620
TAGGTGCAGG GGTACCGGGC CTGGGTGTTG GTGCAGGCGT TCCGGGTTTC GGTGCTGGCG	1680
CGGACGAAGG TGTACGTCGT TCCCTGTCTC CAGAACTGCG TGAAGGTGAC CCGTCCTCTT	1740
CCCAGCACCT GCCGTCTACC CCGTCCTCTC CACGTGTTCC GGGCGCGCTG GCTGCTGCGA	1800
AAGCGGCGAA ATACGGTGCA GCGGTTCCGG GTGTACTGGG CCGTCTGGGT GCTCTGGGCG	1860
GTGTTGGTAT CCCGCGCGGT GTTGTAGGTG CAGGCCCAGC TGCAGCTGCT GCTGCGGCAA	1920
AGGCAGCGGC GAAAGCAGCT CAGTTCGGTC TGGTTGGTGC AGCAGGTCTG GCGGTCTGG	1980
GTGTTGGCGG TCTGGGTGTA CCGGGCGTTG GTGGTCTGGG TGGCATCCCG CCGGCGGCGG	2040
CAGCTAAAGC GGCTAAATAC GGTGCAGCAG GTCTGGGTGG CGTTCTGGGT GGTGCTGGTC	2100
AGTCCCCTT GGGCGGTGTA GCGGCACGTC CCGGTTTCGG TCTGTCCCCG ATCTTCCAG	2160
GCGGTGCATG CCTGGGTAAA GCTTGCAGCC GTAAACGTAA ATAATGATAG	2210

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## (2) INFORMATION FOR SEQ ID NO:2:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 733 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```

Ser Met Gly Gly Val Pro Gly Ala Ile Pro Gly Gly Val Pro Gly Gly
1           5           10           15

Val Phe Tyr Pro Gly Ala Gly Leu Gly Ala Leu Gly Gly Gly Ala Leu
          20           25           30

Gly Pro Gly Gly Lys Pro Leu Lys Pro Val Pro Gly Gly Leu Ala Gly
          35           40           45

Ala Gly Leu Gly Ala Gly Leu Gly Ala Phe Pro Ala Val Thr Phe Pro
          50           55           60

Gly Ala Leu Val Pro Gly Gly Val Ala Asp Ala Ala Ala Tyr Lys
65           70           75           80

Ala Ala Lys Ala Gly Ala Gly Leu Gly Gly Val Pro Gly Val Gly Gly
          85           90           95

Leu Gly Val Ser Ala Gly Ala Val Val Pro Gln Pro Gly Ala Gly Val
          100          105          110

Lys Pro Gly Lys Val Pro Gly Val Gly Leu Pro Gly Val Tyr Pro Gly
          115          120          125

Gly Val Leu Pro Gly Ala Arg Phe Pro Gly Val Gly Val Leu Pro Gly
          130          135          140

Val Pro Thr Gly Ala Gly Val Lys Pro Lys Ala Pro Gly Val Gly Gly
          145          150          155          160

Ala Phe Ala Gly Ile Pro Gly Val Gly Pro Phe Gly Gly Pro Gln Pro

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165	170	175
Gly Val Pro Leu Gly Tyr Pro Ile Lys Ala Pro Lys Leu Pro Gly Gly		
180	185	190
Tyr Gly Leu Pro Tyr Thr Thr Gly Lys Leu Pro Tyr Gly Tyr Gly Pro		
195	200	205
Gly Gly Val Ala Gly Ala Ala Gly Lys Ala Gly Tyr Pro Thr Gly Thr		
210	215	220
Gly Val Gly Pro Gln Ala Ala Ala Ala Ala Ala Lys Ala Ala Ala		
225	230	235 240
Lys Phe Gly Ala Gly Ala Ala Gly Val Leu Pro Gly Val Gly Gly Ala		
245	250	255
Gly Val Pro Gly Val Pro Gly Ala Ile Pro Gly Ile Gly Gly Ile Ala		
260	265	270
Gly Val Gly Thr Pro Ala Ala Ala Ala Ala Ala Ala Ala Lys		
275	280	285
Ala Ala Lys Tyr Gly Ala Ala Ala Gly Leu Val Pro Gly Gly Pro Gly		
290	295	300
Phe Gly Pro Gly Val Val Gly Val Pro Gly Ala Gly Val Pro Gly Val		
305	310	315 320
Gly Val Pro Gly Ala Gly Ile Pro Val Val Pro Gly Ala Gly Ile Pro		
325	330	335
Gly Ala Ala Val Pro Gly Val Val Ser Pro Glu Ala Ala Ala Lys Ala		
340	345	350
Ala Ala Lys Ala Ala Lys Tyr Gly Ala Arg Pro Gly Val Gly Val Gly		
355	360	365
Gly Ile Pro Thr Tyr Gly Val Gly Ala Gly Gly Phe Pro Gly Phe Gly		
370	375	380
Val Gly Val Gly Gly Ile Pro Gly Val Ala Gly Val Pro Ser Val Gly		
385	390	395 400
Gly Val Pro Gly Val Gly Gly Val Pro Gly Val Gly Ile Ser Pro Glu		
405	410	415

- 32 -

Ala Gln Ala Ala Ala Ala Lys Ala Ala Lys Tyr Gly Val Gly Thr  
 420 425 430

Pro Ala Ala Ala Ala Lys Ala Ala Lys Ala Ala Gln Phe Gly  
 435 440 445

Leu Val Pro Gly Val Gly Val Ala Pro Gly Val Gly Val Ala Pro Gly  
 450 455 460

Val Gly Val Ala Pro Gly Val Gly Leu Ala Pro Gly Val Gly Val Ala  
 465 470 475 480

Pro Gly Val Gly Val Ala Pro Gly Val Gly Val Ala Pro Gly Ile Gly  
 485 490 495

Pro Gly Gly Val Ala Ala Ala Lys Ser Ala Ala Lys Val Ala Ala  
 500 505 510

Lys Ala Gln Leu Arg Ala Ala Ala Gly Leu Gly Ala Gly Ile Pro Gly  
 515 520 525

Leu Gly Val Gly Val Gly Val Pro Gly Leu Gly Val Gly Ala Gly Val  
 530 535 540

Pro Gly Leu Gly Val Gly Ala Gly Val Pro Gly Phe Gly Ala Gly Ala  
 545 550 555 560

Asp Glu Gly Val Arg Arg Ser Leu Ser Pro Glu Leu Arg Glu Gly Asp  
 565 570 575

Pro Ser Ser Ser Gln His Leu Pro Ser Thr Pro Ser Ser Pro Arg Val  
 580 585 590

Pro Gly Ala Leu Ala Ala Ala Lys Ala Ala Lys Tyr Gly Ala Ala Val  
 595 600 605

Pro Gly Val Leu Gly Gly Leu Gly Ala Leu Gly Gly Val Gly Ile Pro  
 610 615 620

Gly Gly Val Val Gly Ala Gly Pro Ala Ala Ala Ala Ala Ala Lys  
 625 630 635 640

Ala Ala Ala Lys Ala Ala Gln Phe Gly Leu Val Gly Ala Ala Gly Leu  
 645 650 655

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Gly Gly Leu Gly Val Gly Gly Leu Gly Val Pro Gly Val Gly Gly Leu  
 660 665 670

Gly Gly Ile Pro Pro Ala Ala Ala Ala Lys Ala Ala Lys Tyr Gly Ala  
 675 680 685

Ala Gly Leu Gly Gly Val Leu Gly Gly Ala Gly Gln Phe Pro Leu Gly  
 690 695 700

Gly Val Ala Ala Arg Pro Gly Phe Gly Leu Ser Pro Ile Phe Pro Gly  
 705 710 715 720

Gly Ala Cys Leu Gly Lys Ala Cys Gly Arg Lys Arg Lys  
 725 730

## (2) INFORMATION FOR SEQ ID NO:3:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 698 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Gly Gly Val Pro Gly Ala Ile Pro Gly Gly Val Pro Gly Gly Val Phe  
 1 5 10 15

Tyr Pro Gly Ala Gly Leu Gly Ala Leu Gly Gly Gly Ala Leu Gly Pro  
 20 25 30

Gly Gly Lys Pro Leu Lys Pro Val Pro Gly Gly Leu Ala Gly Ala Gly  
 35 40 45

Leu Gly Ala Gly Leu Gly Ala Phe Pro Ala Val Thr Phe Pro Gly Ala  
 50 55 60

Leu Val Pro Gly Gly Val Ala Asp Ala Ala Ala Tyr Lys Ala Ala  
 65 70 75 80

Lys Ala Gly Ala Gly Leu Gly Gly Val Pro Gly Val Gly Gly Leu Gly

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85	90	95
Val Ser Ala Gly Ala Val Val Pro Gln Pro Gly Ala Gly Val Lys Pro		
100	105	110
Gly Lys Val Pro Gly Val Gly Leu Pro Gly Val Tyr Pro Gly Gly Val		
115	120	125
Leu Pro Gly Ala Arg Phe Pro Gly Val Gly Val Leu Pro Gly Val Pro		
130	135	140
Thr Gly Ala Gly Val Lys Pro Lys Ala Pro Gly Val Gly Gly Ala Phe		
145	150	155
		160
Ala Gly Ile Pro Gly Val Gly Pro Phe Gly Gly Pro Gln Pro Gly Val		
165	170	175
Pro Leu Gly Tyr Pro Ile Lys Ala Pro Lys Leu Pro Gly Gly Tyr Gly		
180	185	190
Leu Pro Tyr Thr Thr Gly Lys Leu Pro Tyr Gly Tyr Gly Pro Gly Gly		
195	200	205
Val Ala Gly Ala Ala Gly Lys Ala Gly Tyr Pro Thr Gly Thr Gly Val		
210	215	220
Gly Pro Gln Ala Ala Ala Ala Ala Ala Ala Lys Ala Ala Ala Lys Phe		
225	230	235
		240
Gly Ala Gly Ala Ala Gly Val Leu Pro Gly Val Gly Gly Ala Gly Val		
245	250	255
Pro Gly Val Pro Gly Ala Ile Pro Gly Ile Gly Gly Ile Ala Gly Val		
260	265	270
Gly Thr Pro Ala Ala Ala Ala Ala Ala Ala Ala Ala Lys Ala Ala		
275	280	285
Lys Tyr Gly Ala Ala Ala Gly Leu Val Pro Gly Gly Pro Gly Phe Gly		
290	295	300
Pro Gly Val Val Gly Val Pro Gly Ala Gly Val Pro Gly Val Gly Val		
305	310	315
		320
Pro Gly Ala Gly Ile Pro Val Val Pro Gly Ala Gly Ile Pro Gly Ala		
325	330	335

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Ala Val Pro Gly Val Val Ser Pro Glu Ala Ala Ala Lys Ala Ala Ala  
 340 345 350

Lys Ala Ala Lys Tyr Gly Ala Arg Pro Gly Val Gly Val Gly Gly Ile  
 355 360 365

Pro Thr Tyr Gly Val Gly Ala Gly Gly Phe Pro Gly Phe Gly Val Gly  
 370 375 380

Val Gly Gly Ile Pro Gly Val Ala Gly Val Pro Ser Val Gly Gly Val  
 385 390 395 400

Pro Gly Val Gly Gly Val Pro Gly Val Gly Ile Ser Pro Glu Ala Gln  
 405 410 415

Ala Ala Ala Ala Ala Lys Ala Ala Lys Tyr Gly Val Gly Thr Pro Ala  
 420 425 430

Ala Ala Ala Ala Lys Ala Ala Ala Lys Ala Ala Gln Phe Gly Leu Val  
 435 440 445

Pro Gly Val Gly Val Ala Pro Gly Val Gly Val Ala Pro Gly Val Gly  
 450 455 460

Val Ala Pro Gly Val Gly Leu Ala Pro Gly Val Gly Val Ala Pro Gly  
 465 470 475 480

Val Gly Val Ala Pro Gly Val Gly Val Ala Pro Gly Ile Gly Pro Gly  
 485 490 495

Gly Val Ala Ala Ala Ala Lys Ser Ala Ala Lys Val Ala Ala Lys Ala  
 500 505 510

Gln Leu Arg Ala Ala Ala Gly Leu Gly Ala Gly Ile Pro Gly Leu Gly  
 515 520 525

Val Gly Val Gly Val Pro Gly Leu Gly Val Gly Ala Gly Val Pro Gly  
 530 535 540

Leu Gly Val Gly Ala Gly Val Pro Gly Phe Gly Ala Val Pro Gly Ala  
 545 550 555 560

Leu Ala Ala Ala Lys Ala Ala Lys Tyr Gly Ala Ala Val Pro Gly Val  
 565 570 575

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Leu Gly Gly Leu Gly Ala Leu Gly Gly Val Gly Ile Pro Gly Gly Val  
                   580                  585                  590

Val Gly Ala Gly Pro Ala Ala Ala Ala Ala Ala Lys Ala Ala Ala  
                   595                  600                  605

Lys Ala Ala Gln Phe Gly Leu Val Gly Ala Ala Gly Leu Gly Gly Leu  
                   610                  615                  620

Gly Val Gly Gly Leu Gly Val Pro Gly Val Gly Gly Leu Gly Gly Ile  
                   625                  630                  635                  640

Pro Pro Ala Ala Ala Ala Lys Ala Ala Lys Tyr Gly Ala Ala Gly Leu  
                   645                  650                  655

Gly Gly Val Leu Gly Gly Ala Gly Gln Phe Pro Leu Gly Gly Val Ala  
                   660                  665                  670

Ala Arg Pro Gly Phe Gly Leu Ser Pro Ile Phe Pro Gly Gly Ala Cys  
                   675                  680                  685

Leu Gly Lys Ala Cys Gly Arg Lys Arg Lys  
                   690                  695

## (2) INFORMATION FOR SEQ ID NO:4:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1983 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: YES

(iv) ANTI-SENSE: NO

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

ATGGGTGGCG TTCCGGGTGC TGTTCGGGT GCGTTCGG GTGGTGTATT CTACCCAGGC 60

GCGGGTTTCG GTGCTGTTCC GGGTGGCGTT GCAGACGCAG CTGCTGCGTA CAAAGCGGCA 120

AAGGCAGGTG CGGGTCTGGG CGGGGTACCA GGTGTTGGCG GTCTGGGTGT ATCTGCTGGC	180
GCAGTTGTTC CGCAGCCGGG TGCAGGTGTA AAACCGGGCA AAGTTCCAGG TGTTGGTCTG	240
CCGGGCGTAT ACCCGGGTTT CGGTGCTGTT CCGGGCGCGC GTTTCACAGG TGTTGGTGTA	300
CTGCCGGGCG TTCCGACCGG TGCAGGTGTT AAACCGAAGG CACCAGGTGT AGGCGGCGCG	360
TTGCGGGTA TCCCGGGTGT TGGCCCGTTC GGTGGTCCGC AGCCAGGCGT TCCGCTGGGT	420
TACCCGATCA AAGCGCCGAA GCTTCCAGGT GGCTACGGTC TGCCGTACAC CACCGGTAAA	480
CTGCCGTACG GCTACGGTCC GGGTGGCGTA GCAGGTGCTG CCGGTAAAGC AGGCTACCCA	540
ACCGGTACTG GTGTTGGTCC GCAGGCTGCT GCGGCAGCTG CCGCGAAGGC AGCAGCAAAA	600
TTGCGCGCGG GTGCAGCGGG TTTCGGTGCT GTTCCGGGCG TAGGTGGTGC TGGCGTTCCG	660
GGTGTTCAG GTGCGATCCC GGGCATCGGT GGTATCGCAG GCGTAGGTAC TCCGGCGGCC	720
GCTGCGGCTG CGGCAGCTGC GGCAGAAAGCA GCTAAATACG GTGCGGCAGC AGGCCTGGTT	780
CCGGGTGGTC CAGGCTTCGG TCCGGGTGTT GTAGGCGTTC CCGGTTCGG TGCTGTTCCG	840
GGCGTAGGTG TTCCAGGTGC GGGCATCCCG GTTGTACCGG GTGCAGGTAT CCCGGGCGCT	900
GCGGGTTTCG GTGCTGTATC CCCGGAAGCG GCAGCTAAGG CTGCTGCGAA AGCTGCGAAA	960
TACGGAGCTC GTCCGGGCGT TGGTGTGGT GGCATCCCGA CCTACGGTGT AGGTGCAGGC	1020
GGTTTCCCAG GTTTCGGCGT TGGTGTGGT GGCATCCCGG GTGTAGCTGG TGTTCCGTCT	1080
GTTGGTGGCG TACCGGGTGT TGGTGGCGTT CCAGGTGTAG GTATCTCCCC GGAAGCGCAG	1140
GCAGCTGCGG CAGCTAAAGC AGCGAAGTAC GGC GTTGGTA CTCCGGCGGC AGCAGCTGCT	1200
AAAGCAGCGG CTAAAGCAGC GCAGTTCGGA CTAGTTCGG GCGTAGGTGT TGC GCCAGGT	1260
GTTGGCGTAG CACCGGGTGT TGGTGTGGT CCGGGCGTAG GTCTGGCACC GGGTGTGGC	1320
GTTGCACCAG GTGTAGGTGT TGC GCCGGC GTTGGTGTAG CACCGGGTAT CCGTCCGGGT	1380
GGCGTTGCGG CTGCTGCGAA ATCTGCTGCG AAGGTTGCTG CGAAAGCGCA GCTGCGTGCA	1440
GCAGCTGGTC TGGGTGCGGG CATCCAGGT CTGGGTGTAG GTGTTGGTGT TCCGGGCCTG	1500

GGTGTAGGTG CAGGGGTACC GGGCCTGGGT GTTGGTGCAG GCGTTCCGGG TTTCGGTGCT 1560  
 GTTCCGGGCG CGCTGGCTGC TGCGAAAGCG GCGAAATACG GTGCTGTTCC GGGTGTA CTG 1620  
 GCGGGTCTGG GTGCTCTGGG CCGTGTTGGT ATCCCGGGCG GTGTTGTAGG TGCAGGCCCA 1680  
 GCTGCAGCTG CTGCTGCGGC AAAGGCAGCG GCGAAAGCAG CTCAGTTCGG TCTGGTTGGT 1740  
 GCAGCAGGTC TGGGCGGTCT GGGTGTTGGC GGTCTGGGTG TACCGGGCGT TGGTGGTCTG 1800  
 GGTGGCATCC CGCCGGCGGC GGCAGCTAAA GCGGCTAAAT ACGGTGCAGC AGGTCTGGGT 1860  
 GGCGTTCTGG GTGGTGCTGG TCAGTTCCCA CTGGGCGGTG TAGCGGCACG TCCGGGTTTC 1920  
 GGTCTGTCCC CGATCTTCCC AGGCGGTGCA TGCCTGGGTA AAGCTTGCGG CCGTAAACGT 1980  
 AAA 1983

## (2) INFORMATION FOR SEQ ID NO:5:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 660 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Met Gly Gly Val Pro Gly Ala Val Pro Gly Gly Val Pro Gly Gly Val  
 1 5 10 15  
 Phe Tyr Pro Gly Ala Gly Phe Gly Ala Val Pro Gly Gly Val Ala Asp  
 20 25 30  
 Ala Ala Ala Ala Tyr Lys Ala Ala Lys Ala Gly Ala Gly Leu Gly Gly  
 35 40 45  
 Val Pro Gly Val Gly Gly Leu Gly Val Ser Ala Gly Ala Val Val Pro  
 50 55 60



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Gln Pro Gly Ala Gly Val Lys Pro Gly Lys Val Pro Gly Val Gly Leu  
 65 70 75 80

Pro Gly Val Tyr Pro Gly Phe Gly Ala Val Pro Gly Ala Arg Phe Pro  
 85 90 95

Gly Val Gly Val Leu Pro Gly Val Pro Thr Gly Ala Gly Val Lys Pro  
 100 105 110

Lys Ala Pro Gly Val Gly Gly Ala Phe Ala Gly Ile Pro Gly Val Gly  
 115 120 125

Pro Phe Gly Gly Pro Gln Pro Gly Val Pro Leu Gly Tyr Pro Ile Lys  
 130 135 140

Ala Pro Lys Leu Pro Gly Gly Tyr Gly Leu Pro Tyr Thr Thr Gly Lys  
 145 150 155 160

Leu Pro Tyr Gly Tyr Gly Pro Gly Gly Val Ala Ala Ala Gly Lys Ala  
 165 170 175

Gly Tyr Pro Thr Gly Thr Gly Val Gly Pro Gln Ala Ala Ala Ala Ala  
 180 185 190

Ala Ala Lys Ala Ala Ala Lys Phe Gly Ala Gly Ala Ala Gly Phe Gly  
 195 200 205

Ala Val Pro Gly Val Gly Gly Ala Gly Val Pro Gly Val Pro Gly Ala  
 210 215 220

Ile Pro Gly Ile Gly Gly Ile Ala Gly Val Gly Thr Pro Ala Ala Ala  
 225 230 235 240

Ala Ala Ala Ala Ala Ala Ala Lys Ala Ala Lys Tyr Gly Ala Ala Ala  
 245 250 255

Gly Leu Val Pro Gly Gly Pro Gly Phe Gly Pro Gly Val Val Gly Val  
 260 265 270

Pro Gly Phe Gly Ala Val Pro Gly Val Gly Val Pro Gly Ala Gly Ile  
 275 280 285

Pro Val Val Pro Gly Ala Gly Ile Pro Gly Ala Ala Gly Phe Gly Ala  
 290 295 300

Val Ser Pro Glu Ala Ala Ala Lys Ala Ala Ala Lys Ala Ala Lys Tyr

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305		310		315		320
Gly Ala Arg Pro Gly Val Gly Val Gly Gly Ile Pro Thr Tyr Gly Val						
	325		330		335	
Gly Ala Gly Phe Phe Pro Gly Phe Gly Val Gly Val Gly Gly Ile Pro						
	340		345		350	
Gly Val Ala Gly Val Pro Ser Val Gly Gly Val Pro Gly Val Gly Gly						
	355		360		365	
Val Pro Gly Val Gly Ile Ser Pro Glu Ala Gln Ala Ala Ala Ala Ala						
	370		375		380	
Lys Ala Ala Lys Tyr Gly Val Gly Thr Pro Ala Ala Ala Ala Ala Lys						
	385		390		395	400
Ala Ala Ala Lys Ala Ala Gln Phe Gly Leu Val Pro Gly Val Gly Val						
	405		410		415	
Ala Pro Gly Val Gly Val Ala Pro Gly Val Gly Val Ala Pro Gly Val						
	420		425		430	
Gly Leu Ala Pro Gly Val Gly Val Ala Pro Gly Val Gly Val Ala Pro						
	435		440		445	
Gly Val Gly Val Ala Pro Gly Ile Gly Pro Gly Gly Val Ala Ala Ala						
	450		455		460	
Ala Lys Ser Ala Ala Lys Val Ala Ala Lys Ala Gln Leu Arg Ala Ala						
	465		470		475	480
Ala Gly Leu Gly Ala Gly Ile Pro Gly Leu Gly Val Gly Val Gly Val						
	485		490		495	
Pro Gly Leu Gly Val Gly Ala Gly Val Pro Gly Leu Gly Val Gly Ala						
	500		505		510	
Gly Val Pro Gly Phe Gly Ala Val Pro Gly Ala Leu Ala Ala Ala Lys						
	515		520		525	
Ala Ala Lys Tyr Gly Ala Val Pro Gly Val Leu Gly Gly Leu Gly Ala						
	530		535		540	
Leu Gly Gly Val Gly Ile Pro Gly Gly Val Val Gly Ala Gly Pro Ala						
	545		550		555	560

Ala Ala Ala Ala Ala Ala Lys Ala Ala Ala Lys Ala Ala Gln Phe Gly  
565 570 575

Leu Val Gly Ala Ala Gly Leu Gly Gly Leu Gly Val Gly Gly Leu Gly  
580 585 590

Val Pro Gly Val Gly Gly Leu Gly Gly Ile Pro Pro Ala Ala Ala Ala  
595 600 605

Lys Ala Ala Lys Tyr Gly Ala Ala Gly Leu Gly Gly Val Leu Gly Gly  
610 615 620

Ala Gly Gln Phe Pro Leu Gly Gly Val Ala Ala Arg Pro Gly Phe Gly  
625                      630                      635                      640

Leu Ser Pro Ile Phe Pro Gly Gly Ala Cys Leu Gly Lys Ala Cys Gly  
645 650 655

Arg Lys Arg Lys  
660

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 441 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: double  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: YES

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

TCCGCCATGG	GAGGTGTTCC	GGGCGCGCTG	GCTGCTGCGA	AAGCGGCGAA	ATACGGTGCA	60
GCGGTTCCGG	GTGTA CTGGG	CGGTCTGGGT	GCTCTGGGCG	GTGTTGGTAT	CCCGGGCGGT	120
GTTGTAGGTG	CAGGCCCAGC	TGCAGCTGCT	GCTGCGGCAA	AGGCAGCGGC	GAAAGCAGCT	180

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CAGTTCGGTC TGGTTGGTGC AGCAGGTGTG GGCGGTCTGG GTGTTGGCGG TCTGGGTGTA 240  
 CCGGGCGTTG GTGGTCTGGG TGGCATCCCG CCGGCGGCGG CAGCTAAAGC GGCTAAATAC 300  
 GGTGCAGCAG GTCTGGGTGG CGTTCTGGGT GGTGCTGGTC AGTTCCCACT GGGCGGTGTA 360  
 GCGGCACGTC CGGGTTTCGG TCTGTCCCCG ATCTTCCCAG GCGGTGCATG CCTGGGTAAA 420  
 GCTTGCGGCC GTAAACGTAA A 441

## (2) INFORMATION FOR SEQ ID NO:7:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 147 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Ser Ala Met Gly Gly Val Pro Gly Ala Leu Ala Ala Ala Lys Ala Ala  
 1 5 10 15  
 Lys Tyr Gly Ala Ala Val Pro Gly Val Leu Gly Gly Leu Gly Ala Leu  
 20 25 30  
 Gly Gly Val Gly Ile Pro Gly Gly Val Val Gly Ala Gly Pro Ala Ala  
 35 40 45  
 Ala Ala Ala Ala Ala Lys Ala Ala Ala Lys Ala Ala Gln Phe Gly Leu  
 50 55 60  
 Val Gly Ala Ala Gly Leu Gly Gly Leu Gly Val Gly Gly Leu Gly Val  
 65 70 75 80  
 Pro Gly Val Gly Gly Leu Gly Gly Ile Pro Pro Ala Ala Ala Ala Lys  
 85 90 95  
 Ala Ala Lys Tyr Gly Ala Ala Gly Leu Gly Gly Val Leu Gly Gly Ala  
 100 105 110

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Gly Gln Phe Pro Leu Gly Gly Val Ala Ala Arg Pro Gly Phe Gly Leu  
 115 120 125

Ser Pro Ile Phe Pro Gly Gly Ala Cys Leu Gly Lys Ala Cys Gly Arg  
 130 135 140

Lys Arg Lys  
 145

## (2) INFORMATION FOR SEQ ID NO:8:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 600 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: double
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: YES

(iv) ANTI-SENSE: NO

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

TCCGCCATGG GAGCTCTGGT AGGCCTGGGC GTACCGGGCC TGGGTGTTGG TGCAGGCGTT	60
CCGGGTTTCG GTGCTGGCGC GGACGAAGGT GTACGTCGTT CCCTGTCTCC AGAACTGCGT	120
GAAGGTGACC CGTCCTCTTC CCAGCACCTG CCGTCTACCC CGTCCTCTCC ACGTGTTCGG	180
GGCGCGCTGG CTGCTGCGAA AGCGGCGAAA TACGGTGCAG CGGTTCCGGG TGTACTGGGC	240
GGTCTGGGTG CTCTGGGCGG TGTGGTATC CCGGGCGGTG TTGTAGGTGC AGGCCAGCT	300
GCAGCTGCTG CTGCGGCAAA GGCAGCGGCG AAAGCAGCTC AGTTCGGTCT GGTGGTGCA	360
GCAGGTCTGG GCGGTCTGGG TGTGGCGGT CTGGGTGTAC CGGGCGTTGG TGGTCTGGGT	420
GGCATCCCCG CGGCGGCGGC AGCTAAAGCG GCTAAATACG GTGCAGCAGG TCTGGGTGGC	480
GTTCTGGGTG GTGCTGGTCA GTTCCCACTG GCGGTGTAG CGGCACGTCC GGGTTTCGGT	540

CTGTCCCCGA TCTTCCCAGG CGGTGCATGC CTGGGTAAAG CTTGCGGCCG TAAACGTAAA 600

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 200 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

Ser	Ala	Met	Gly	Ala	Leu	Val	Gly	Leu	Gly	Val	Pro	Gly	Leu	Gly	Val	1	5	10	15
Gly	Ala	Gly	Val	Pro	Gly	Phe	Gly	Ala	Gly	Ala	Asp	Glu	Gly	Val	Arg	20	25	30	
Arg	Ser	Leu	Ser	Pro	Glu	Leu	Arg	Glu	Gly	Asp	Pro	Ser	Ser	Ser	Gln	35	40	45	
His	Leu	Pro	Ser	Thr	Pro	Ser	Ser	Pro	Arg	Val	Pro	Gly	Ala	Leu	Ala	50	55	60	
Ala	Ala	Lys	Ala	Ala	Lys	Tyr	Gly	Ala	Ala	Val	Pro	Gly	Val	Leu	Gly	65	70	75	80
Gly	Leu	Gly	Ala	Leu	Gly	Gly	Val	Gly	Ile	Pro	Gly	Gly	Val	Val	Gly	85	90	95	
Ala	Gly	Pro	Ala	Ala	Ala	Ala	Ala	Ala	Ala	Lys	Ala	Ala	Ala	Lys	Ala	100	105	110	
Ala	Gln	Phe	Gly	Leu	Val	Gly	Ala	Ala	Gly	Leu	Gly	Gly	Leu	Gly	Val	115	120	125	
Gly	Gly	Leu	Gly	Val	Pro	Gly	Val	Gly	Gly	Leu	Gly	Gly	Ile	Pro	Pro	130	135	140	

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(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

Gly Ala Asp Glu Gly Val Arg Arg Ser Leu Ser Pro Glu Leu Arg Glu  
1 5 10 15

Gly Asp Pro Ser Ser Ser Gln His Leu Pro Ser Thr Pro Ser Ser Pro  
20 25 30

Arg Phe

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 216 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Ala Ala Ala Gly Leu Gly Ala Gly Ile Pro Gly Leu Gly Val Gly Val  
1                5                10                15

Gly Val Pro Gly Leu Gly Val Gly Ala Gly Val Pro Gly Leu Gly Val  
20 25 30

Gly Ala Gly Val Pro Gly Phe Gly Ala Gly Ala Asp Glu Gly Val Arg  
35 40 45

Arg Ser Leu Ser Pro Glu Leu Arg Glu Gly Asp Pro Ser Ser Ser Gln  
50 55 60

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His Leu Pro Ser Thr Pro Ser Ser Pro Arg Val Pro Gly Ala Leu Ala  
 65 70 75 80

Ala Ala Lys Ala Ala Lys Tyr Gly Ala Ala Val Pro Gly Val Leu Gly  
 85 90 95

Gly Leu Gly Ala Leu Gly Gly Val Gly Ile Pro Gly Gly Val Val Gly  
 100 105 110

Ala Gly Pro Ala Ala Ala Ala Ala Ala Lys Ala Ala Ala Lys Ala  
 115 120 125

Ala Gln Phe Gly Leu Val Gly Ala Ala Gly Leu Gly Gly Leu Gly Val  
 130 135 140

Gly Gly Leu Gly Val Pro Gly Val Gly Gly Leu Gly Gly Ile Pro Pro  
 145 150 155 160

Ala Ala Ala Ala Lys Ala Ala Lys Tyr Gly Ala Ala Gly Leu Gly Gly  
 165 170 175

Val Leu Gly Gly Ala Gly Gln Phe Pro Leu Gly Gly Val Ala Ala Arg  
 180 185 190

Pro Gly Phe Gly Leu Ser Pro Ile Phe Pro Gly Gly Ala Cys Leu Gly  
 195 200 205

Lys Ala Cys Gly Arg Lys Arg Lys  
 210 215

## (2) INFORMATION FOR SEQ ID NO:15:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 183 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

Ala Ala Ala Gly Leu Gly Ala Gly Ile Pro Gly Leu Gly Val Gly Val



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Ala Ala Ala Ala Lys Ala Ala Lys Tyr Gly Ala Ala Gly Leu Gly Gly  
 145 150 155 160

Val Leu Gly Gly Ala Gly Gln Phe Pro Leu Gly Gly Val Ala Ala Arg  
 165 170 175

Pro Gly Phe Gly Leu Ser Pro Ile Phe Pro Gly Gly Ala Cys Leu Gly  
 180 185 190

Lys Ala Cys Gly Arg Lys Arg Lys  
 195 200

## (2) INFORMATION FOR SEQ ID NO:10:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 60 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Gly Ile Pro Pro Ala Ala Ala Lys Ala Ala Lys Tyr Gly Ala Ala  
 1 5 10 15

Gly Leu Gly Gly Val Leu Gly Gly Ala Gly Gln Phe Pro Leu Gly Gly  
 20 25 30

Val Ala Ala Arg Pro Gly Phe Gly Leu Ser Pro Ile Phe Pro Gly Gly  
 35 40 45

Ala Cys Leu Gly Lys Ala Cys Gly Arg Lys Arg Lys  
 50 55 60

## (2) INFORMATION FOR SEQ ID NO:11:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 47 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

```
Gly Ala Ala Gly Leu Gly Gly Val Leu Gly Gly Ala Gly Gln Phe Pro
1           5           10           15

Leu Gly Gly Val Ala Ala Arg Pro Gly Phe Gly Leu Ser Pro Ile Phe
          20           25           30

Pro Gly Gly Ala Cys Leu Gly Lys Ala Cys Gly Arg Lys Arg Lys
      35           40           45
```

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 34 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

```
Gly Ala Asp Glu Gly Val Arg Arg Ser Leu Ser Pro Glu Leu Arg Glu
1           5           10           15

Gly Asp Pro Ser Ser Ser Gln His Leu Pro Ser Thr Pro Ser Ser Pro
      20           25           30

Arg Val
```

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 34 amino acids
- (B) TYPE: amino acid

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1	5	10	15
Gly Val Pro Gly Leu Gly Val Gly Ala Gly Val Pro Gly Leu Gly Val			
20	25	30	
Gly Ala Gly Val Pro Gly Phe Gly Ala Val Pro Gly Ala Leu Ala Ala			
35	40	45	
Ala Lys Ala Ala Lys Tyr Gly Ala Ala Val Pro Gly Val Leu Gly Gly			
50	55	60	
Leu Gly Ala Leu Gly Gly Val Gly Ile Pro Gly Gly Val Val Gly Ala			
65	70	75	80
Gly Pro Ala Ala Ala Ala Ala Ala Lys Ala Ala Ala Lys Ala Ala			
85	90	95	
Gln Phe Gly Leu Val Gly Ala Ala Gly Leu Gly Gly Leu Gly Val Gly			
100	105	110	
Gly Leu Gly Val Pro Gly Val Gly Gly Leu Gly Gly Ile Pro Pro Ala			
115	120	125	
Ala Ala Ala Lys Ala Ala Lys Tyr Gly Ala Ala Gly Leu Gly Gly Val			
130	135	140	
Leu Gly Gly Ala Gly Gln Phe Pro Leu Gly Gly Val Ala Ala Arg Pro			
145	150	155	160
Gly Phe Gly Leu Ser Pro Ile Phe Pro Gly Gly Ala Cys Leu Gly Lys			
165	170	175	
Ala Cys Gly Arg Lys Arg Lys			
180			

THE CLAIMS:

1. A human tropoelastin derivative or an amino acid sequence variant thereof, wherein the derivative or  
5 variant has elastin-like properties.
2. A human tropoelastin derivative or an amino acid sequence variant thereof, wherein the derivative or  
variant has macro-molecular binding properties.  
10
3. A derivative or variant thereof according to claim 2 wherein the macro-molecular binding properties include the ability to bind glycosaminoglycans.
- 15 4. A human tropoelastin derivative or an amino acid sequence variant thereof, wherein the derivative or variant has elastin-like properties and macro-molecular binding properties.
- 20 5. A polynucleotide encoding a derivative or variant thereof of any one of claims 1 to 4.
6. A tropoelastin derivative comprising the amino acid sequence of SHEL $\delta$ modified, or an amino acid sequence  
25 variant of the derivative comprising the amino acid sequence of SHEL $\delta$ modified.
7. A tropoelastin derivative according to claim 6 comprising SEQ ID NO: 5.  
30
8. A polynucleotide encoding a tropoelastin derivative, the derivative comprising the amino acid sequence of SHEL $\delta$ modified or an amino acid sequence  
variant of the derivative comprising the amino acid  
35 sequence of SHEL $\delta$ modified.

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9. A polynucleotide according to claim 8 comprising  
SEQ ID NO: 4.

5 10. A synthetic polynucleotide encoding a  
tropoelastin derivative, the derivative comprising the  
amino acid sequence of SHEL $\delta$ 26A or an amino acid sequence  
variant of the derivative comprising the amino acid  
sequence of SHEL $\delta$ 26A.

10 11. A synthetic polynucleotide according to claim  
10, the polynucleotide comprising the sequence of from  
nucleotide position 1 to 1676 contiguous with the sequence  
of from nucleotide position 1775 to 2210 of SEQ ID NO: 1.

15 12. An amino acid sequence variant of the derivative  
comprising the amino acid sequence of SHEL $\delta$ 26A.

20 13. An amino acid sequence variant according to  
claim 12 comprising SEQ ID NO:3.

25 14. A tropoelastin derivative comprising the amino  
acid sequence of SHELgamma, or an amino acid sequence  
variant of the derivative comprising the amino acid  
sequence of SHELgamma.

30 15. A tropoelastin derivative according to claim 14  
comprising SEQ ID NO:9.

35 16. A polynucleotide encoding a tropoelastin  
derivative, the derivative comprising the amino acid  
sequence of the derivative SHELgamma, or an amino acid  
sequence variant of the derivative comprising the amino  
acid sequence of SHELgamma.

40 17. A polynucleotide sequence according to claim 16  
comprising SEQ ID NO:8.

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18. A tropoelastin derivative comprising the amino acid sequence of SHELgamma excluding exon 26A, or an amino acid sequence variant of the derivative comprising the amino acid sequence of SHELgamma excluding exon 26A.

5

19. A tropoelastin derivative according to claim 18 comprising SEQ ID NO:7.

20. A polynucleotide encoding a tropoelastin derivative, the derivative comprising the amino acid sequence of SHELgamma excluding exon 26A or an amino acid sequence variant of the derivative comprising the amino acid sequence of SHELgamma excluding exon 26A.

21. A polynucleotide sequence according to claim 20 comprising SEQ ID NO: 6.

22. A tropoelastin derivative comprising the amino acid sequence of SHEL31-36, or an amino acid sequence variant of the derivative comprising the amino acid sequence of SHEL31-36.

23. A tropoelastin derivative according to claim 22 comprising SEQ ID NO: 10.

25

24. A polynucleotide encoding a tropoelastin derivative, the derivative comprising the amino acid sequence of SHEL31-36 or an amino acid sequence variant of the derivative comprising the amino acid sequence of SHEL31-36.

30

25. A polynucleotide according to claim 24, the polynucleotide comprising the sequence of from nucleotide position 2022 to 2210 of SEQ ID NO: 1.

35

26. A tropoelastin derivative comprising the amino acid sequence of SHEL32-36, or an amino acid sequence variant of the derivative comprising the amino acid

sequence of SHEL32-36.

27. A tropoelastin derivative according to claim 26 comprising SEQ ID NO: 11.

5

28. A polynucleotide encoding a tropoelastin derivative, the derivative comprising the amino acid sequence of SHEL32-36 or an amino acid sequence variant of the derivative comprising the amino acid sequence of SHEL32-36.

10

29. A polynucleotide according to claim 28, the polynucleotide comprising the sequence of from nucleotide position 2061 to 2210 of SEQ ID NO: 1.

15

30. A tropoelastin derivative comprising the amino acid sequence of peptide 26A, or an amino acid sequence variant of the derivative comprising the amino acid sequence of peptide 26A.

20

31. A tropoelastin derivative according to claim 30 comprising SEQ ID NO: 12 or SEQ ID NO: 13.

32. A polynucleotide encoding a tropoelastin derivative, the derivative comprising the amino acid sequence of peptide 26A or an amino acid sequence variant of the derivative comprising the amino acid sequence of peptide 26A.

25

33. A polynucleotide according to claim 32, the polynucleotide comprising the sequence of from nucleotide position 1677 to 1774 of SEQ ID NO: 1.

30

34. A tropoelastin derivative comprising the amino acid sequence of SHEL26-36, or an amino acid sequence variant of the derivative comprising the amino acid sequence of SHEL26-26.

35

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35. A tropoelastin derivative according to claim 34 comprising SEQ ID NO: 14.

5 36. A polynucleotide encoding a tropoelastin derivative, the derivative comprising the amino acid sequence of SHEL26-36 or an amino acid sequence variant of the derivative comprising the amino acid sequence of SHEL26-36.

10 37. A polynucleotide according to claim 36, the polynucleotide comprising the sequence of from nucleotide position 1554 to 2210 of SEQ ID NO: 1.

15 38. A tropoelastin derivative comprising the amino acid sequence of SHEL26-26 excluding exon 26A, or an amino acid sequence variant of the derivative comprising the amino acid sequence of SHEL26-26 excluding exon 26A.

20 39. A tropoelastin derivative according to claim 38 comprising SEQ ID NO: 15.

25 40. A polynucleotide encoding a tropoelastin derivative, the derivative comprising the amino acid sequence of SHEL26-26 excluding exon 26A or an amino acid sequence variant of the derivative of SHEL26-26 excluding exon 26A.

30 41. A polynucleotide according to claim 40, the polynucleotide comprising the sequence of from nucleotide position 1554 to 1676 contiguous with the sequence of from nucleotide position 1776 to 2210 of SEQ ID NO: 1.

35 42. A vector comprising a polynucleotide according to any one of claims 5, 8, 9, 16, 17, 20, 21, 24, 25, 28, 29, 32, 33, 36, 37, 40 or 41, or a synthetic polynucleotide according to claim 10 or 11.

43. The vector according to claim 42 wherein the



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polynucleotide or synthetic polynucleotide is operatively linked to a promoter or enhancer regulatory sequence.

44. The vector according to claim 42 or 43 wherein the polynucleotide or synthetic polynucleotide is operatively linked to a nucleotide sequence, the nucleotide sequence encoding a further amino acid sequence.

45. A cell containing a vector according to any one of claims 42 to 44.

46. A method for producing a derivative of tropoelastin or an amino acid sequence variant of the derivative, the method comprising:

- (a) providing a vector according to any one of claims 42 to 44;
- (b) introducing the vector into a cell;
- (c) maintaining the cell in conditions suitable for expression of the vector; and
- (d) isolating the tropoelastin derivative or variant.

47. A tropoelastin derivative or variant produced by the method of claim 46.

48. A transgenic non-human animal containing a vector according to any one of claims 42 to 44, or a polynucleotide according to any one of claims 5, 8, 9, 16, 17, 20, 21, 24, 25, 28, 29, 32, 33, 36, 37, 40 or 41, or a synthetic polynucleotide according to claim 10 or 11.

49. A tropoelastin derivative or variant of the derivative produced by a transgenic animal according to claim 48

50. method for producing a tropoelastin derivative or a variant of the derivative according to any one of

- 56 -

claims 1-4, 6, 7, 12-15, 18, 19, 22, 23, 26, 27, 30, 31, 34, 35, 38 or 39, the method comprising producing the tropoelastin derivative or variant by solid-phase peptide synthesis.

5

51. A tropoelastin derivative or variant produced by the method of claim 50.

52. A formulation comprising at least one tropoelastin derivative or variant of the derivative according to any one of 1-4, 6, 7, 12-15, 18, 19, 22, 23, 26, 27, 30, 31, 34, 35, 38, 39, 47 or 49, together with a pharmaceutically acceptable carrier or diluent.

53. An expression product comprising a tropoelastin derivative or variant of the derivative according to any one of claims 1-4, 6, 7, 12-15, 18, 19, 22, 23, 26, 27, 30, 31, 34, 35, 38, 39, 47 or 49, and a further amino acid sequence.

20

54. An expression product according to claim 53 wherein the tropoelastin derivative comprises the amino acid sequence of peptide 26A, or an amino acid sequence variant of the derivative comprising the amino acid sequence of peptide 26A.

25

55. A polynucleotide encoding an expression product according to claims 53 or 54.

56. A vector comprising the polynucleotide according to claim 55.

30

57. A cell containing a vector according to claim 56.

35

58. A method for producing an expression product according to claim 52 or 54, the method comprising:

(a) providing a vector according to claim 56;

- 57 -

- (b) introducing the vector into a cell;
- (c) maintaining the cell in conditions suitable for expression of the vector; and
- (d) isolating the expression product.

5

59. An expression product produced by the method of claim 58.

60. An transgenic non-human animal containing a vector according to claim 56 or a polynucleotide according to claim 55.

61. An expression product produced by a transgenic animal according to claim 60.

15

62. A formulation comprising at least one expression product according to any of claims 53, 54, 59 or 61, together with a pharmaceutically acceptable carrier or diluent.

20

63. A hybrid molecule comprising a biological polymer wherein the polymer is linked to a tropoelastin derivative comprising the amino acid sequence of peptide 26A or an amino acid sequence variant of the derivative comprising peptide 26A.

25

64. A hybrid molecule according to claim 63 wherein the biological polymer is a protein.

65. A hybrid molecule according to claim 64 wherein in the protein is selected from the group consisting of cytokines, growth factors and antibodies.

30

66. A hybrid molecule according to claim 63 wherein the biological polymer is selected from the group consisting of lipids, sugars and nucleic acids.

35

67. A polynucleotide sequence encoding a hybrid molecule according to claim 64.

68. A vector comprising a polynucleotide sequence according to claim 67.

5           69. A cell containing a vector according to claim 68.

70. A method for producing a hybrid molecule according to claim 64, the method comprising:

- 10           (a) providing a vector according to claim 68;  
             (b) introducing the vector into a cell;  
             (c) maintaining the cell in conditions suitable for expression of the vector; and  
             (d) isolating the hybrid molecule.

15

71. A hybrid molecule produced by the method of claim 70.

20           72. A transgenic non-human animal containing a vector according to claim 68 or a polynucleotide according to claim 67.

73. A hybrid molecule produced by a transgenic animal according to claim 72.

25

74. A hybrid molecule comprising a synthetic polymer linked to peptide 26A or a variant of peptide 26A.

30           75. A formulation comprising at least one hybrid molecule according to any of claims 63-65, 71, 73 and 74, together with a pharmaceutically acceptable carrier or diluent.

35           76. A cross linked complex, the complex comprising at least one of the following:

- (i) at least one derivative or variant of the derivative according to any of 1-4, 6, 7, 12-15, 18, 19, 22, 23, 26, 27, 30, 31, 34, 35, 38, 39, 47

or 49;

(ii) at least expression product according to any of claims 53, 54, 58 or 61; and

5 (iii) at least one hybrid molecule according to any of claims 63-65, 71, 73 or 74.

77. An implant, the implant comprising at least one of the following:

10 (i) at least one derivative or variant of the derivative according to any of 1-4, 6, 7, 12-15, 18, 19, 22, 23, 26, 27, 30, 31, 34, 35, 38, 39, 47 or 49;

(ii) at least expression product according to any of claims 53, 54, 58 or 61; and

15 (iii) at least one hybrid molecule according to any of claims 63-65, 71, 73 or 74.

78. A method of imparting glycosaminoglycan binding activity to a biological polymer comprising the step of  
20 linking a tropoelastin derivative comprising the amino acid sequence of peptide 26A, or an amino acid sequence variant of the derivative comprising the amino acid sequence of peptide 26A with the biological polymer.

25 79. A method of deleting glycosaminoglycan binding activity from a biological polymer comprising the step of deleting a tropoelastin derivative comprising the amino acid sequence of peptide 26A, or an amino acid sequence variant of the derivative comprising the amino acid  
30 sequence of peptide 26A from the biological polymer.

80. The method of claim 66 or 67 wherein the biological polymer is a protein.

35 81. A formulation comprising a tropoelastin derivative or variant of the derivative and a synthetic or biological polymer.

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1 GATCCATGGGTGGCGTTCCGGGTGCTATCCCGGGTGGCGTTCCGGGTGGTGTATTCTACC 60  
GTACCCACCGCAAGGCCCACGATAGGGCCACCGCAAGGCCACCACATAAGATGG  
S M G G V P G A I P G G V P G G V F Y P

61 CAGGCGCGGGTCTGGGTGCACTGGGCGGTGGTGGCTGGGCCCGGGTGGTAAACCGCTGA 120  
GTCCGCGCCAGACCCACGTGACCGGCCACCACGCGACCCGGGCCCCACCATTTGGCGACT  
G A G L G A L G G G A L G P G G K P L K

121 AACCGGTTCCAGGCGGTCTGGCAGGTGCTGGTCTGGGTGCAGGTCTGGGCGCGTTCCCGG 180  
TTGGCCAAGGTCCGCCAGACCGTCCACGACCAGACCCACGTCCAGACCCGCGCAAGGGCC  
P V P G G L A G A G L G A G L G A F P A

181 CGGTTACCTTCCCGGGTGCTCTGGTTCCGGGTGGCGTTGCAGACGCAGCTGCTGCGTACA 240  
GCCAATGGAAGGGCCCACGAGACCAAGGCCACCGCAACGTCTGCGTCGACGACGCATGT  
V T F P G A L V P G G V A D A A A A Y K

241 AAGCGGCAAAGGCAGGTGCGGGTCTGGGCGGGGTACCAGGTGTTGGCGGTCTGGGTGTAT 300  
TTCGCCGTTTCCGTCCACGCCCAGACCCGCCCCATGGTCCACAACGCCAGACCCACATA  
A A K A G A G L G G V P G V G G L G V S

301 CTGCTGGCGCAGTTGTTCCGCGCGCGGGTGCAGGTGTAAAACCGGGCAAAGTTCCAGGTG 360  
GACGACCGCGTCAACAAGGCGTCGGCCCCACGTCCACATTTTGGCCCGTTTCAAGGTCCAC  
A G A V V P Q P G A G V K P G K V P G V

361 TTGGTCTGCCGGGCGTATACCCGGGTGGTGTCTGCGGGGCGCGGTTTCCCAGGTGTTG 420  
AACCAGACGGCCCGCATATGGGGCCACCACAAGACGGCCCGCGCGCAAAGGGTCCACAAC  
G L P G V Y P G G V L P G A R F P G V G

Figure 1(1)

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421 GTGTACTGCCGGGCGTTCCGACCGGTGCAGGTGTTAAACCGAAGGCACCAGGTGTAGGCG 480  
CACATGACGGCCCGCAAGGCTGGCCACGTCCACAATTTGGCTTCCGTGGTCCACATCCGC  
V L P G V P T G A G V K P K A P G V G G

481 GCGCGTTGCGGGGTATCCCGGGTGTGGCCCGTTCGGTGGTCCGCGAGCCAGGCGTTCCGC 540  
CGCGCAAGCGCCCATAGGGCCACAAACCGGGCAAGCCACCAGGCGTCGGTCCGCAAGGCG  
A F A G I P G V G P F G G P Q P G V P L

541 TGGGTTACCGGATCAAAGCGCCGAAGCTTCCAGGTGGCTACGGTCTGCCGTACACCACCG 600  
ACCCAATGGGCTAGTTTCGCGGCTTCGAAGGTCCACCGATGCCAGACGGCATGTGGTGGC  
G Y P I K A P K L P G G Y G L P Y T T G

601 GTAACTGCCGTACGGCTACGGTCCGGGTGGCGTAGCAGGTGCTGCGGGTAAAGCAGGCT 660  
CATTTGACGGCATGCCGATGCCAGGCCCACCGCATCGTCCACGACGCCCATTTCGTCCGA  
K L P Y G Y G P G G V A G A A G K A G Y

661 ACCCAACCGGTACTGGTGTGGTCCGCGAGGCTGCTGCGGCAGCTGCGGGCGAAGGCAGCAG 720  
TGGGTGGCCATGACCACAACCGGCGTCCGACGACGCCGTGACGCGCGCTTCCGTCTC  
P T G T G V G P Q A A A A A A A K A A A

721 CAAAATTCGGCGCGGGTGCAGCGGGTGTCTGCCGGGCGTAGGTGGTGTGGCGTTCCGC 780  
GTTTAAAGCCGCGCCACGTGCGCCACAAGACGGCCCGCATCCACCACGACCGCAAGGCC  
K F G A G A A G V L P G V G G A G V P G

781 GTGTTCCAGGTGCGATCCCGGGCATCGGTGGTATCGCAGGCGTAGGTACTCCGGCGGGCCG 840  
CACAGGTCCACGCTAGGGCCCGTAGCCACCATAGCGTCCGCGATCCATGAGGCCGCCGGC  
V P G A I P G I G G I A G V G T P A A A

841 CTGCGGCTGCGGCAGCTGCGGGCGAAAGCAGCTAAATACGGTGCGGCAGCAGGCCTGGTTC 900  
GACGCCGACGCGCTCGACGCGCGCTTTCGTGATTTATGCCACGCGCTCGTCCGGACCAAG  
A A A A A A A K A A K Y G A A A G L V P

Figure 1(2)

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901 CGGGTGGTCCAGGCTTCGGTCCGGGTGTTGTAGGCGTTCCGGGTGCTGGTGTTCGGGGCG 960  
GCCACCAAGGTCCGAAGCCAGGCCCAACATCCGCAAGGCCACGACCACAAGGCCCGC  
G G P G F G P G V V G V P G A G V P G V

961 TAGGTGTTCCAGGTGCGGGCATCCCGGTTGTACCGGGTGTCAGGTATCCCGGGCGCTGCGG 1020  
ATCCACAAGGTCCACGCCCGTAGGGCCACATGGCCACGTCCATAGGGCCCGCGACGCC  
G V P G A G I P V V P G A G I P G A A V

1021 TTCCAGGTGTTGTATCCCCGGAAGCGGCAGCTAAGGCTGCTGCGAAAGCTGCGAAATACG 1080  
AAGGTCCACAACATAGGGGCCTTCGCCGTCGATTCCGACGACGCTTTCGACGCTTTATGC  
P G V V S P E A A A K A A A K A A K Y G

1081 GAGCTCGTCCGGGCGTTGGTGTGGTGGGCATCCCGACCTACGGTGTAGGTGCAGGCGGTT 1140  
CTCGAGCAGGCCCGCAACCACAACCACCGTAGGGCTGGATGCCACATCCACGTCCGCCAA  
A R P G V G V G G I P T Y G V G A G G F

1141 TCCCAGGTTTCGGCGTTGGTGTGGTGGGCATCCCGGGTGTAGCTGGTGTTCGCTCTGTTG 1200  
AGGGTCCAAAGCCGCAACCACAACCACCGTAGGGCCACATCGACCACAAGGCAGACAAC  
P G F G V G V G G I P G V A G V P S V G

1201 GTGGCGTACCGGGTGTGGTGGCGTTCCAGGTGTAGGTATCTCCCCGGAAGCGCAGGCAG 1260  
CACCGCATGGGCCACAACCACCGCAAGGTCCACATCCATAGAGGGGCCTTCGCGTCCGTC  
G V P G V G G V P G V G I S P E A Q A A

1261 CTGCGGCAGCTAAAGCAGCGAAGTACGGCGTTGGTACTCCGGCGGCAGCAGCTGCTAAAG 1320  
GACGCCGTCGATTTCGTCGCTTCATGCCGCAACCATGAGGCCCGCGTCGTCGACGATTTC  
A A A K A A K Y G V G T P A A A A A K A

1321 CAGCGGCTAAAGCAGCGCAGTTCCGGACTAGTTCCGGGCGTAGGTGTTGCGCCAGGTGTTG 1380  
GTCGCCGATTTCGTCGCGTCAAGCCTGATCAAGGCCCGCATCCACAACGCGGTCCACAAC  
A A K A A Q F G L V P G V G V A P G V G

Figure 1(3)



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1381 GCGTAGCACCGGGTGTGGTGTGCTCCGGGCGTAGGTCTGGCACCGGGTGTGGCGTTG 1440  
CGCATCGTGGCCCACAACCACAACGAGGCCCGCATCCAGACCGTGGCCCACAACCAGCAAC  
V A P G V G V A P G V G L A P G V G V A

1441 CACCAGGTGTAGGTGTGGCGCCGGGCGTTGGTGTAGCACCGGGTATCGGTCCGGGTGGCG 1500  
GTGGTCCACATCCACAACGCGGCCCGCAACCACATCGTGGCCCATAGCCAGGCCACCGC  
P G V G V A P G V G V A P G I G P G G V

1501 TTGCGGCTGCTGCGAAATCTGCTGCGAAGGTTGCTGCGAAAGCGCAGCTGCGTGCAGCAG 1560  
AACGCCGACGACGCTTTAGACGACGCTTCCAACGACGCTTTCGCGTCGACGCACGTCGTC  
A A A A K S A A K V A A K A Q L R A A A

1561 CTGGTCTGGGTGCGGGCATCCCAGGTCTGGGTGTAGGTGTGGTGTTCGGGGCCTGGGTG 1620  
GACCAGACCCACGCCCCGTAGGGTCCAGACCCACATCCACAACCACAAGGCCCCGACCCAC  
G L G A G I P G L G V G V G V P G L G V

1621 TAGGTGCAGGGGTACCGGGCCTGGGTGTGGTGCAGGCGTTCCGGGTTTCGGTGCTGGCG 1680  
ATCCACGTCCCCATGGCCCGGACCCACAACCACGTCCGCAAGGCCCAAAGCCACGACCGC  
G A G V P G L G V G A G V P G F G A G A

1681 CGGACGAAGGTGTACGTGCTTCCCTGTCTCCAGAACTGCGTGAAGGTGACCCGTCTCTT 1740  
GCCTGCTTCCACATGCAGCAAGGGACAGAGGTCTTGACGCACTTCCACTGGGCAGGAGAA  
D E G V R R S L S P E L R E G D P S S S

1741 CCCAGCACCTGCCGTCTACCCCGTCTCTCCACGTGTTCCGGGCGCGCTGGCTGCTGCGA 1800  
GGGTGCTGGACGGCAGATGGGGCAGGAGAGGTGCACAAGGCCCGCGCGACCGACGACGCT  
Q H L P S T P S S P R V P G A L A A A K

1801 AAGCGGCGAAATACGGTGCAGCGGTTCCGGGTGTACTGGGCGGTCTGGGTGCTCTGGGCG 1860  
TTCGCCGCTTTATGCCACGTCCGCAAGGCCACATGACCCGCCAGACCCACGAGACCCGC  
A A K Y G A A V P G V L G G L G A L G G

Figure 1(4)

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1861 GTGTTGGTATCCCGGGCGGTGTTGTAGGTGCAGGCCAGCTGCAGCTGCTGCTGCGGCAA 1920  
CACAAACCATAGGGCCCGCCACAACATCCACGTCCGGGTGCGACGTCGACGACGACGCCGTT  
V G I P G G V V G A G P A A A A A A A K

1921 AGGCAGCGGCGAAAGCAGCTCAGTTCGGTCTGGTTGGTGCAGCAGGTCTGGGCGGTCTGG 1980  
TCCGTCGCCGCTTTTCGTGCGAGTCAAGCCAGACCAACCACGTCCAGACCCGCCAGACC  
A A A K A A Q F G L V G A A G L G G L G

1981 GTGTTGGCGGTCTGGGTGTACCGGGCGTTGGTGGTCTGGGTGGCATCCCGCCGGCGGCGG 2040  
CACAAACCGCCAGACCCACATGGCCCCGCAACCACCAGACCCACCGTAGGGCGGCGCCGCC  
V G G L G V P G V G G L G G I P P A A A

2041 CAGCTAAAGCGGCTAAATACGGTGCAGCAGGTCTGGGTGGCGTTCTGGGTGGTGCTGGTC 2100  
GTCGATTTCGCCGATTTATGCCACGTCTCCAGACCCACCGCAAGACCCACCACGACCAG  
A K A A K Y G A A G L G G V L G G A G Q

2101 AGTTCCCACTGGGCGGTGTAGCGGCACGTCCGGGTTTCGGTCTGTCCCCGATCTTCCAG 2160  
TCAAGGGTGACCCGCCACATCGCCGTGCAGGCCCAAAGCCAGACAGGGGCTAGAAGGGTC  
F P L G G V A A R P G F G L S P I F P G

2161 GCGGTGCATGCCTGGGTAAAGCTTGCGGGCCGTAAACGTAAATAATGATAG 2210  
CGCCACGTACGGACCCATTTCGAACGCCGGCATTTCGATTTATTACTATCCTAG  
G A C L G K A C G R K R K \* \* \*

Figure 1(5)

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1  GGVPGAIPGGVPGGVFYPGAGLGALGGGALGPGGKPLKPVPGGLAGAGLG  50
  |||
1  GGVPGAIPGGVPGGVFYPGAGLGALGGGALGPGGKPLKPVPGGLAGAGLG  50
  |||
51  AGLGAFFAVTFPGALVPGGVADAAAAAYKAAKAGAGLGGVPGVGGVGVEAG  100
  |||
51  AGLGAFFAVTFPGALVPGGVADAAAAAYKAAKAGAGLGGVPGVGGVGVEAG  100
  |||
101 AVVPPQPGAGVKGKVPGVGLPGVYPGGVLPGARFPGVGVLPVPTGAGVK  150
  |||
101 AVVPPQPGAGVKGKVPGVGLPGVYPGGVLPGARFPGVGVLPVPTGAGVK  150
  |||
151 PKAPGVGGAFAGIPGVGPFGGPQPGVPLGYPIKAPKLPGGYGLPYTTGKL  200
  |||
151 PKAPGVGGAFAGIPGVGPFGGPQPGVPLGYPIKAPKLPGGYGLPYTTGKL  200
  |||
201 PYGYGPGGVAGAGKAGYPTGTGVGPQAAAAAANKAAKFGAGAAAGVLP  250
  |||
201 PYGYGPGGVAGAGKAGYPTGTGVGPQAAAAAANKAAKFGAGAAAGVLP  250
  |||
251 VGGAGVPGVPGAIPGIGGLAGVGTAAAAAANKAAKYGAAGLVPG  300
  |||
251 VGGAGVPGVPGAIPGIGGLAGVGTAAAAAANKAAKYGAAGLVPG  300
  |||
301 PGFGPGVVGVPAGVPGVGPAGIPVVPAGIPGAAPVGVVSPAAAAKA  350
  |||
301 PGFGPGVVGVPAGVPGVGPAGIPVVPAGIPGAAPVGVVSPAAAAKA  350
  |||
351 AAKAAKYGARPGVGVGGIPTYGVGAGGFPFGVGVGGIPGVAGVPSVGGV  400
  |||
351 AAKAAKYGARPGVGVGGIPTYGVGAGGFPFGVGVGGIPGVAGVPSVGGV  400
  |||
401 PGVGGVPGVGISPEAQAAAAAANKAAKYGVGTPAAAAAANKAAQAQFGLVPG  450
  |||
401 PGVGGVPGVGISPEAQAAAAAANKAAKYGVGTPAAAAAANKAAQAQFGLVPG  450
  |||
451 VGVAPGVGVAPGVGVAPGVGLAPGVGVAPGVGVAPGVGVAPGIGPGGVAA  500
  |||
451 VGVAPGVGVAPGVGVAPGVGLAPGVGVAPGVGVAPGVGVAPGIGPGGVAA  500
  |||
501 AAKSAAKVAAKAQLRAAAGLGAGIPGLGVGVGPGLGVGAGVPGLGVGAG  550
  |||
501 AAKSAAKVAAKAQLRAAAGLGAGIPGLGVGVGPGLGVGAGVPGLGVGAG  550
  |||
551 VPGFGAGADEGVRRSLSPKLRREGDPSSSQHLPSTPSSPRVPGALAAAKAA  600
  |||
551 VPGFGA.....VPGALAAAKAA  567
  |||
601 KYGAAPVPGVVGGLGALGGVGIPGGVVGAGPAAAAAANKAAKAQAQFGLVG  650
  |||
568 KYGAAPVPGVVGGLGALGGVGIPGGVVGAGPAAAAAANKAAKAQAQFGLVG  617
  |||
651 AAGLGGLGVGGIGVPGVGGGLGGIPAAAAAANKYGAAGLGGVGGAGQFP  700
  |||
618 AAGLGGLGVGGIGVPGVGGGLGGIPAAAAAANKYGAAGLGGVGGAGQFP  667
  |||
701 LGGVAARPGFGLSPIFPGGACLGKACGRKRK  731
  |||
668 LGGVAARPGFGLSPIFPGGACLGKACGRKRK  698
  |||

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Figure 2(1)

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1 ATGGGTGGCGTTCCGGGTGCTGTTCCGGGTGGCGTTCCGGGTGGTGTATT 50
1 MetGlyGlyValProGlyAlaValProGlyGlyValProGlyGlyValPh 17
51 CTACCCAGGCGCGGGTTTCGGTGTCTGTTCCGGGTGGCGTTGCAGACGCAG 100
18 eTyrProGlyAlaGlyPheGlyAlaValProGlyGlyValAlaAspAlaA 34
101 CTGCTGCGTACAAAGCGGCAGAGTCCGGGTCTGGGCGGGGTACCA 150
35 laAlaAlaTyrTysAlaAlaIysAlaGlyAlaGlyLeuGlyGlyValPro 50
151 GGTGTTGGCGGTCTGGGTGTATCTGCTGGCGCAGTTGTTCCGCAGCGGG 200
51 GlyValGlyGlyLeuGlyValSerAlaGlyAlaValValProGlnProG 67
201 TGCAGGTGTAAACCGGGCAAGTTCAGGTGTTGGTCTGCGGGGCGTAT 250
68 yAlaGlyValLysProGlyLysValProGlyValGlyLeuProGlyValT 84
251 ACCCGGGTTTCGGTGTCTGTTCCGGGCGCGCGTTTCCAGGTGTTGGTGT 300
85 yrProGlyPheGlyAlaValProGlyAlaArgTheProGlyValGlyVal 100
301 CTGCCGGGCGTTCCGACCGGTGCAGGTGTAAACCGAAGGCACCAGGTGT 350
101 LeuProGlyValProThrGlyAlaGlyValLysProLysAlaProGlyVa 117
351 AGGCGGCGCGTTCCGGGTATCCCGGGTGTGGCCCGTTCCGGTGGTCCGC 400
118 lGlyGlyAlaPheAlaGlyIleProGlyValGlyProPheGlyGlyProG 134
401 AGCCAGGCGTTCCGCTGGGTACCCGATCAAAGCGCCGAAGCTTCCAGGT 450
135 lnProGlyValProLeuGlyTyrProIleLysAlaProLysLeuProGly 150
451 GGCTACGGTCTGCCGTACACCACCGGTAAACTGCCGTACGGCTACGGTCC 500
151 GlyTyrGlyLeuProTyrThrThrGlyLysLeuProTyrGlyTyrGlyPr 167
501 GGGTGGCGTAGCAGGTGCTGCGGGTAAAGCAGGCTACCCAAACCGGTACTG 550
168 oGlyGlyValAlaGlyAlaAlaGlyLysAlaGlyTyrProThrGlyThrG 184
551 GTGTTGGTCCGCAGGCTGCTGCGGCAGCTGCGCGAAGGCAGCAGCAAA 600
185 lyValGlyProGlnAlaAlaAlaAlaAlaAlaAlaAlaLysAlaAlaLys 200
601 TTCGGCGCGGGTGCAGCGGGTTTCGGTGTCTGTTCCGGGCGTAGGTGGTGC 650
201 PheGlyAlaGlyAlaAlaGlyPheGlyAlaValProGlyValGlyGlyAl 217
651 TGGCGTTCCGGGTGTTCCAGGTGCGATCCCGGGCATCGGTGGTATCGCAG 700
218 aGlyValProGlyValProGlyAlaIleProGlyIleGlyGlyIleAlaG 234
701 GCGTAGGTACTCCGGCGGCGCTGCGGCTGCGGCAGCTGCGGCGAAGCA 750
235 lyValGlyThrProAlaAlaAlaAlaAlaAlaAlaAlaAlaAlaLysAla 250

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Figure 3(1)

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751 GCTAATAACGGTGCAGCAGGCGCTGGTTCGGGGTGGTCCAGGCTTCGG 800  
|||  
251 AlaLysTyrGlyAlaAlaAlaGlyLeuValProGlyGlyProGlyPheGly 267  
801 TCCGGGTGTGTAGGCGTTCCGGGTTTCGGTGTCTGTTCGGGGCGTAGGTG 850  
|||  
268 yProGlyValValGlyValProGlyPheGlyAlaValProGlyValGlyV 284  
851 TTCCAGGTGCAGGCGATCCGGTTGTACCGGGTGCAGGTATCCCGGGCGCT 900  
|||  
285 alProGlyAlaGlyIleProValValProGlyAlaGlyIleProGlyAla 300  
901 GCGGGTTTCGGTGTCTGTATCCCGGAAGCGGCAGCTAGGCTGTCTGGAA 950  
|||  
301 AlaGlyPheGlyAlaValSerProGluAlaAlaAlaLysAlaAlaAlaLy 317  
951 AGCTGCGAAATACGGAGCTCGTCCGGGCGTGGTGTGGTGGCATCCCGA 1000  
|||  
318 sAlaAlaLysTyrGlyAlaArgProGlyValGlyValGlyGlyIleProT 334  
1001 CCTACGGTGTAGGTGCAGGCGGTTTCCCGAGTTTTCGGCGTTGGTGTGGT 1050  
|||  
335 hrTyrGlyValGlyAlaGlyGlyPheProGlyPheGlyValGlyValGly 350  
1051 GGCATCCCGGGTGTAGCTGGTGTTCGGTCTGTGGTGGCGTACCGGGTGT 1100  
|||  
351 GlyIleProGlyValAlaGlyValProSerValGlyGlyValProGlyVa 367  
1101 TGGTGGCGTTCCAGGTGTAGGTATCTCCCGGAAGCGCAGGCAGCTGCGG 1150  
|||  
368 lGlyGlyValProGlyValGlyIleSerProGluAlaGlnAlaAlaAlaA 384  
1151 CAGCTAAAGCAGCGAAGTACGGCGTTGGTACTCCGGCGGCAGCAGCTGCT 1200  
|||  
385 laAlaLysAlaAlaLysTyrGlyValGlyThrProAlaAlaAlaAlaAla 400  
1201 AAAGCAGCGGCTAAAGCAGCGCAGTTCCGACTAGTTCCGGGCGTAGGTGT 1250  
|||  
401 LysAlaAlaAlaLysAlaAlaGlnPheGlyLeuValProGlyValGlyVa 417  
1251 TCGCCAGGTGTGGCGTAGCACCAGGTGTGGTGTGTCTCCGGGCGTAG 1300  
|||  
418 lAlaProGlyValGlyValAlaProGlyValGlyValAlaProGlyValG 434  
1301 GTCTGSCACCGGGTGTGGCGTTGCACCAGGTGTAGGTGTTCGCGCGGC 1350  
|||  
435 lyLeuAlaProGlyValGlyValAlaProGlyValGlyValAlaProGly 450  
1351 GTTGGTGTAGCACCAGGTATCCGGTCCGGGTGGCGTTGCGGCTGCTGCGAA 1400  
|||  
451 ValGlyValAlaProGlyIleGlyProGlyGlyValAlaAlaAlaAlaLy 467  
1401 ATCTGCTGCGAAGGTTGCTGCGAAGCGCAGCTGCGTGCAGCAGCTGCTC 1450  
|||  
468 sSerAlaAlaLysValAlaAlaLysAlaGlnLeuArgAlaAlaAlaGlyL 484  
1451 TGGGTGCGGCGATCCCGAGTCTGGGTGTAGGTGTGGTGTTCGGGCGCTG 1500  
|||  
485 euGlyAlaGlyIleProGlyLeuGlyValGlyValGlyValProGlyLeu 500

Figure 3(2)

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```

1501 GGTGTAGGTGCAGGGGTACCGGGCCTGGGTGTTGGTGCAGGCGTTCCGGG 1550
    |||
501 GlyValGlyAlaGlyValProGlyLeuGlyValGlyAlaGlyValProG 517
1551 TTTCGGTGTCTGTTCCGGGCGCGCTGGCTGCTGCGAAGCGGCGAATACG 1600
    |||
518 yPheGlyAlaValProGlyAlaLeuAlaAlaAlaAlaLysAlaAlaLysTyrG 534
1601 GTGCTGTTCCGGGTGTACTGGGCGGCTCTGGGTGCTCTGGGCGGTGTTGGT 1650
    |||
535 lyAlaValProGlyValLeuGlyGlyLeuGlyAlaLeuGlyGlyValGly 550
1651 ATCCCGGGCGGTGTGTAGGTGCAGGCCAGCTGCAGCTGCTGCTGCGGC 1700
    |||
551 ileProGlyGlyValValGlyAlaGlyProAlaAlaAlaAlaAlaAla 567
1701 AAAGGCAGCGGCGAAGCAGCTCAGTTCCGGTCTGGTTGGTGCAGCAGGTC 1750
    |||
568 aLysAlaAlaAlaLysAlaAlaGlnPheGlyLeuValGlyAlaAlaGlyL 584
1751 TGGGCGGTCTGGGTGTTGGCGGTCTGGGTGTACCGGGCGTGGTGGTCTG 1800
    |||
585 euGlyGlyLeuGlyValGlyGlyLeuGlyValProGlyValGlyGlyLeu 600
1801 GGTGGCATCCCGCCGGCGGGCGGCAGCTAAAGCGGCTAAATACGGTGCAGC 1850
    |||
601 GlyGlyIleProProAlaAlaAlaAlaLysAlaAlaLysTyrGlyAlaAl 617
1851 AGGTCTGGGTGGCGTTCTGGGTGGTGTCTGGTCAGTTCCCACTGGGCGGTG 1900
    |||
618 aGlyLeuGlyGlyValLeuGlyGlyAlaGlyGlnPheProLeuGlyGlyV 634
1901 TAGCGGCACGTCCGGGTTTCCGGTCTGTCCCGCATCTCCCGAGGCGGTGCA 1950
    |||
635 alAlaAlaArgProGlyPheGlyLeuSerProIlePheProGlyGlyAla 650
1951 TGCCTGGGTAAAGCTTGGGCGGTAAACGTAAA 1983
    |||
651 CysLeuGlyLysAlaCysGlyArgLysArgLys 661

```

Figure 3(3)

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1 ATGGGTGGCGTTCCGGGTGCTGTTCGGGTGGCGTTCCGGGTGGTGATT 50  
1 ATGGGTGGCGTTCCGGGTGCTATCCGGGTGGCGTTCCGGGTGGTGATT 50  
51 CTACCCAGGCGCGGGTTTCGGTGC..... 74  
51 CTACCCAGGCGCGGGTCTGGGTGCACTGGGCGGTGGTGCGCTGGGCCCGG 100  
:  
:  
75 .....TGT 77  
151 GGTGCAGGTCTGGGCGCGTTCCGGCGGGTTACCTTCCGGGTGCTCTGGT 200  
78 TCCGGGTGGCGTTGTCAGACGAGCTGCTGCGTACAAAGCGGCAAAGGCAG 127  
201 TCCGGGTGGCGTTGTCAGACGAGCTGCTGCGTACAAAGCGGCAAAGGCAG 250  
128 GTGCGGGTCTGGGCGGGGTACCAGGTGTTGGCGGTCTGGGTGTATCTGCT 177  
251 GTGCGGGTCTGGGCGGGGTACCAGGTGTTGGCGGTCTGGGTGTATCTGCT 300  
178 GGCGCAGTTGTTCCGCAGCCGGGTGTCAGGTGTAAACCGGGCAAAGTTCC 227  
301 GGCGCAGTTGTTCCGCAGCCGGGTGTCAGGTGTAAACCGGGCAAAGTTCC 350  
228 AGGTGTTGGTCTGCCGGGCGTATACCGGGTTTCGGTGCTGTTCCGGGCG 277  
351 AGGTGTTGGTCTGCCGGGCGTATACCGGGT...GGTGTCTGCCGGGCG 397  
278 CGCGTTTCCAGGTGTTGGTGTACTGCCGGGCGTTCCGACCGGTGTCAGGT 327  
398 CGCGTTTCCAGGTGTTGGTGTACTGCCGGGCGTTCCGACCGGTGTCAGGT 447  
328 GTTAAACCGAAGGCACCAGGTGTAGGCGGCGCGTTCCGCGGTATCCCGG 377  
448 GTTAAACCGAAGGCACCAGGTGTAGGCGGCGCGTTCCGCGGTATCCCGG 497  
378 TGTGCGCCCGTTCCGTGGTCCGCAGCCAGGCGTTCCGCTGGGTACCCGA 427  
498 TGTGCGCCCGTTCCGTGGTCCGCAGCCAGGCGTTCCGCTGGGTACCCGA 547  
428 TCAAAGCGCCGAAGCTTCCAGGTGGCTACGGTCTGCCGTACACCACGGT 477  
548 TCAAAGCGCCGAAGCTTCCAGGTGGCTACGGTCTGCCGTACACCACGGT 597  
478 AAACGTCCGTACCGCTACGGTCCGGGTGGCGTAGCAGGTGCTGCCGGTAA 527  
598 AAACGTCCGTACCGCTACGGTCCGGGTGGCGTAGCAGGTGCTGCCGGTAA 647  
528 AGCAGGCTACCCAAACCGGTACTGGTGTGGTCCGCAGGCTGCTGCCGCG 577  
648 AGCAGGCTACCCAAACCGGTACTGGTGTGGTCCGCAGGCTGCTGCCGCG 697  
578 CTGCGGCGAAGGCAGCAGCAAAATTCGGCGCGGGTGCAGCGGGTTTCGGT 627  
698 CTGCGGCGAAGGCAGCAGCAAAATTCGGCGCGGGTGCAGCG.....GGT 741  
628 GCTGTTCCGGCGGTAGGTGGTGTGGCGTTCCGGGTGTTCCAGGTGCGAT 677  
742 GTTCTGCCGGGCGTAGGTGGTGTGGCGTTCCGGGTGTTCCAGGTGCGAT 791

Figure 4(1)

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678 CCGGGGCATCGGTGGTATCGCAGGCGTAGGTACTCCGGCGGCCGCTGCGG 727  
|||  
792 CCGGGGCATCGGTGGTATCGCAGGCGTAGGTACTCCGGCGGCCGCTGCGG 841  
|||  
728 CTGCGGCAGCTGCGGCGAAGCAGCTAATAACGGTGCGGCAGCAGGCCTG 777  
|||  
842 CTGCGGCAGCTGCGGCGAAGCAGCTAATAACGGTGCGGCAGCAGGCCTG 891  
|||  
778 GTTCCGGGTGGTCCAGGCTTCGGTCCGGGTGTTGTAGGCGTTCCGGGTTT 827  
|||  
892 GTTCCGGGTGGTCCAGGCTTCGGTCCGGGTGTTGTAGGCGTTCCGGGT.. 939  
|||  
828 CGGTGCTGTTCCGGGCGTAGGTGTTCCAGGTGCGGGCATCCCGGTTGTAC 877  
|||  
940 .GCTGGTGTTCGGGCGTAGGTGTTCCAGGTGCGGGCATCCCGGTTGTAC 988  
|||  
878 CGGGTGCAAGGTATCCCGGGCGCTGCGGGTTTCGGTGCTGTATCCCGGAA 927  
|||  
989 CGGGTGCAAGGTATCCCGGGCGCTGCGGGTTCCAGGTGTGTATCCCGGAA 1038  
|||  
928 GCGGCAGCTAAGGCTGCTGCGAAGCTGCGAATAAGGAGCTCGTCCGGG 977  
|||  
1039 GCGGCAGCTAAGGCTGCTGCGAAGCTGCGAATAAGGAGCTCGTCCGGG 1088  
|||  
978 CGTTGGTGTGTTGGTGGCATCCCGACCTACGGTGTAGGTGCAGGCGGTTTC 1027  
|||  
1089 CGTTGGTGTGTTGGTGGCATCCCGACCTACGGTGTAGGTGCAGGCGGTTTC 1138  
|||  
1028 CAGGTTTCGGCGTTGGTGTGTTGGTGGCATCCCGGGTGTAGCTGGTGTTCG 1077  
|||  
1139 CAGGTTTCGGCGTTGGTGTGTTGGTGGCATCCCGGGTGTAGCTGGTGTTCG 1188  
|||  
1078 TCTGTGTTGGTGGCGTACCGGGTGTGTTGGTGGCGTTCCAGGTGTAGGTATCTC 1127  
|||  
1189 TCTGTGTTGGTGGCGTACCGGGTGTGTTGGTGGCGTTCCAGGTGTAGGTATCTC 1238  
|||  
1128 CCGGAAGCGCAGGCAGCTGCGGCAGCTAAGCAGCGAAGTACGGCGTTG 1177  
|||  
1239 CCGGAAGCGCAGGCAGCTGCGGCAGCTAAGCAGCGAAGTACGGCGTTG 1288  
|||  
1178 GTACTCCGGCGGCAGCAGCTGCTAAGCAGCGGCTAAGCAGCGCAGTTTC 1227  
|||  
1289 GTACTCCGGCGGCAGCAGCTGCTAAGCAGCGGCTAAGCAGCGCAGTTTC 1338  
|||  
1228 GGACTAGTTCCGGGCGTAGGTGTTGCGCCAGGTGTTGGCGTAGCACCGGG 1277  
|||  
1339 GGACTAGTTCCGGGCGTAGGTGTTGCGCCAGGTGTTGGCGTAGCACCGGG 1388  
|||  
1278 TGTGTTGGTGTGCTCCGGGCGTAGGTCTGGCCAGGTGTTGGCGTAGCAC 1327  
|||  
1389 TGTGTTGGTGTGCTCCGGGCGTAGGTCTGGCCAGGTGTTGGCGTAGCAC 1438  
|||  
1328 CAGGTGTAGGTGTTGCGCCGGGCGTTGGTGTAGCACCGGGTATCGGTCCG 1377  
|||  
1439 CAGGTGTAGGTGTTGCGCCGGGCGTTGGTGTAGCACCGGGTATCGGTCCG 1488  
|||  
1378 GGTGGCGTTGCGGCTGCTGCGAATCTGCTGCGAAGGTGCTGCGAAGGC 1427  
|||  
1489 GGTGGCGTTGCGGCTGCTGCGAATCTGCTGCGAAGGTGCTGCGAAGGC 1538  
|||

Figure 4(2)



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1428 GCAGCTGCGTGCAGCAGCTGGTCTGGGTGCGGGCATCCAGGTCTGGGTG 1477  
1539 GCAGCTGCGTGCAGCAGCTGGTCTGGGTGCGGGCATCCAGGTCTGGGTG 1588  
1478 TAGGTGTTGGTGTTCGGGGCTGGGTGTAGGTGCAGGGGTACCGGGCCTG 1527  
1589 TAGGTGTTGGTGTTCGGGGCTGGGTGTAGGTGCAGGGGTACCGGGCCTG 1638  
1528 GGTGTTGGTGCAGGCGTTCCGGGTTTCGGTGC ..... 1559  
1639 GGTGTTGGTGCAGGCGTTCCGGGTTTCGGTGCCTGGCGCGGACGAAGGTGT 1688  
:  
:  
1560 .....TGTTCCGGGCGCGCTGGCT 1578  
1739 AGCACCTGCCGTCTACCCCGTCTCTCCACGTGTTCCGGGCGCGCTGGCT 1788  
1579 GCTGCGAAGCGGCGAAATACGGT...GCTGTTCCGGGTGTACTGGGCGG 1625  
1789 GCTGCGAAGCGGCGAAATACGGTGCAGCGGTTCGGGTGTACTGGGCGG 1838  
1626 TCTGGGTGCTCTGGGCGGTGTGGTATCCCGGGCGGTGTGTAGGTGCAG 1675  
1839 TCTGGGTGCTCTGGGCGGTGTGGTATCCCGGGCGGTGTGTAGGTGCAG 1888  
1676 GCCCAGCTGCAGCTGCTGCTGCGGCAAAGGCAGCGGCGAAAGCAGCTCAG 1725  
1889 GCCCAGCTGCAGCTGCTGCTGCGGCAAAGGCAGCGGCGAAAGCAGCTCAG 1938  
1726 TTGGGTCTGGTGTGGTGCAGCAGGTCTGGGCGGTCTGGGTGTGGGCGGTCT 1775  
1939 TTGGGTCTGGTGTGGTGCAGCAGGTCTGGGCGGTCTGGGTGTGGGCGGTCT 1988  
1776 GGGTGTACCGGGCGTTGGTGGTCTGGGTGGCATCCCGCGGCGGCGGCAG 1825  
1989 GGGTGTACCGGGCGTTGGTGGTCTGGGTGGCATCCCGCGGCGGCGGCAG 2038  
1826 CTAAGCGGCTAAATACGGTGCAGCAGGTCTGGGTGGCGTTCTGGGTGGT 1875  
2039 CTAAGCGGCTAAATACGGTGCAGCAGGTCTGGGTGGCGTTCTGGGTGGT 2088  
1876 GCTGGTCAAGTTCCTACTGGGCGGTGTAGCGGCACGTCCGGGTTTCGGTCT 1925  
2089 GCTGGTCAAGTTCCTACTGGGCGGTGTAGCGGCACGTCCGGGTTTCGGTCT 2138  
1926 GTCCCGATCTTCCAGGCGGTGCATGCCCTGGGTAAAGCTTGCGGCCGTA 1975  
2139 GTCCCGATCTTCCAGGCGGTGCATGCCCTGGGTAAAGCTTGCGGCCGTA 2188  
1976 AACGTAAATAATGATAG 1992  
2189 AACGTAAATAATGATAG 2205

Figure 4(3)

**Figure 5(1)**

**Figure 5(2)**

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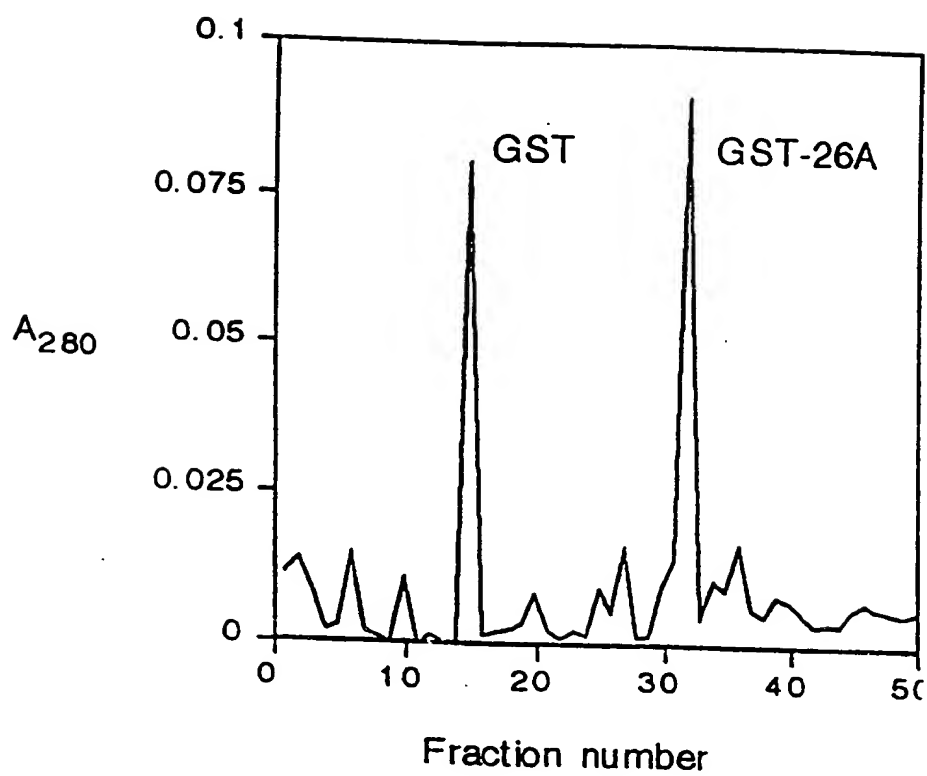


Fig. 6(a)

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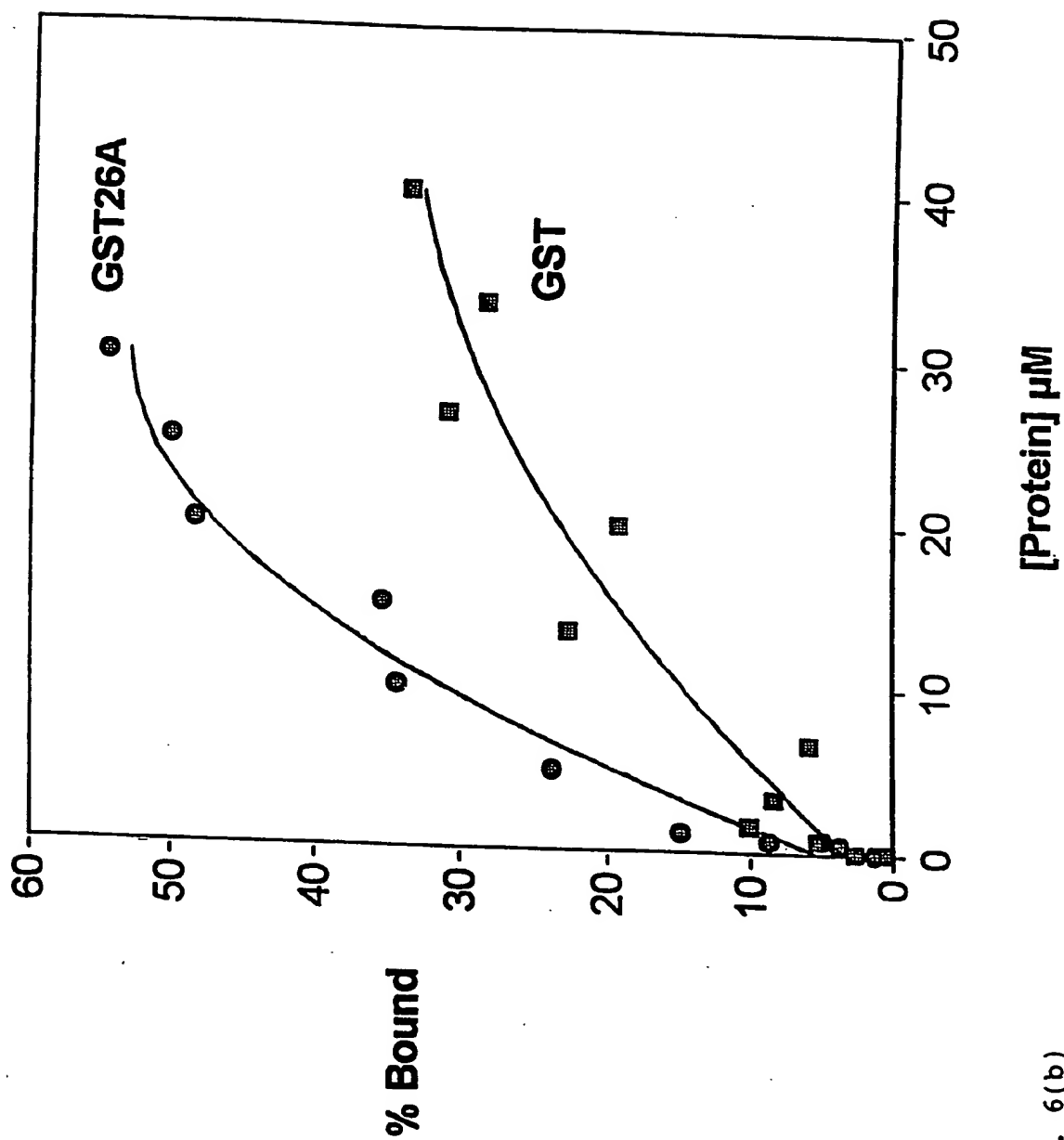


Fig. 6(b)

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948 TCCGCCATGGGAGGTGTTCCGGGCGCGCTGGCTGCTGCGAAAGCGGCGAA 997  
|||||  
1 SerAlaMetGlyGlyValProGlyAlaLeuAlaAlaLysAlaAlaLy 17

998 ATACGGTGCAGCGGTTCGGGTGTACTGGGCGGTCTGGGTGCTCTGGGCG 1047  
|||||  
18 sTyrGlyAlaAlaValProGlyValLeuGlyGlyLeuGlyAlaLeuGlyG 34

1048 GTGTTGGTATCCCGGGCGGTGTTGTAGGTGCAGGCCAGCTGCAGCTGCT 1097  
|||||  
35 lyValGlyIleProGlyGlyValValGlyAlaGlyProAlaAlaAlaAla 50

1098 GCTGCGGCAAAGGCAGCGGCGAAAGCAGCTCAGTTCGGTCTGGTTGGTGC 1147  
|||||  
51 AlaAlaAlaLysAlaAlaAlaLysAlaAlaGlnPheGlyLeuValGlyAl 67

1148 AGCAGGTCTGGGCGGTCTGGGTGTTGGCGGTCTGGGTGTACCGGGCGTTG 1197  
|||||  
68 aAlaGlyLeuGlyGlyLeuGlyValGlyGlyLeuGlyValProGlyValG 84

1198 GTGGTCTGGGTGGCATCCCGCCGGCGGCGGCAGCTAAAGCGGCTAAATAC 1247  
|||||  
85 lyGlyLeuGlyGlyIleProProAlaAlaAlaAlaLysAlaAlaLysTyr 100

1248 GGTGCAGCAGGTCTGGGTGGCGTTCTGGGTGGTGTGCTGGTCAGTTCCCACT 1297  
|||||  
101 GlyAlaAlaGlyLeuGlyGlyValLeuGlyGlyAlaGlyGlnPheProLe 117

1298 GGGCGGTGTAGCGGCACGTCCGGGTTTCGGTCTGTCCCCGATCTTCCCAG 1347  
|||||  
118 uGlyGlyValAlaAlaArgProGlyPheGlyLeuSerProIlePheProG 134

1348 GCGGTGCATGCCTGGGTAAAGCTTGCGGCCGTAAACGTAAA 1388  
|||||  
135 lyGlyAlaCysLeuGlyLysAlaCysGlyArgLysArgLys 147

Figure 7

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948 TCCGCCATGGGAGCTCTGGTAGGCCTGGGCGTACCGGGCCTGGGTGTTGG 997  
|||||  
1 SerAlaMetGlyAlaLeuValGlyLeuGlyValProGlyLeuGlyValGl 17

998 TGCAGGCGTTCCGGGTTTCGGTGCTGGCGCGGACGAAGGTGTACGTCGTT 1047  
|||||  
18 yAlaGlyValProGlyPheGlyAlaGlyAlaAspGluGlyValArgArgS 34

1048 CCCTGTCTCCAGAACTGCGTGAAGGTGACCCGTCCTCTTCCCAGCACCTG 1097  
|||||  
35 erLeuSerProGluLeuArgGluGlyAspProSerSerSerGlnHisLeu 50

1098 CCGTCTACCCCGTCCTCTCCACGTGTTCCGGGCGCGCTGGCTGCTGCGAA 1147  
|||||  
51 ProSerThrProSerSerProArgValProGlyAlaLeuAlaAlaAlaLy 67

1148 AGCGGCGAAATACGGTGCAGCGGTTCCGGGTGTACTGGGCGGTCTGGGTG 1197  
|||||  
66 sAlaAlaLysTyrGlyAlaAlaValProGlyValLeuGlyGlyLeuGlyA 84

1198 CTCTGGGCGGTGTTGGTATCCCGGGCGGTGTTGTAGGTGCAGGCCCCAGCT 1247  
|||||  
85 laLeuGlyGlyValGlyIleProGlyGlyValValGlyAlaGlyProAla 100

Figure 8(1).

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1248 GCAGCTGCTGCTGCGGCAAAGGCAGCGGCGAAAGCAGCTCAGTTCGGTCT 1297  
|||||  
101 AlaAlaAlaAlaAlaAlaLysAlaAlaAlaLysAlaAlaGlnPheGlyLe 117  
1298 GGTGGGTGCAGCAGGTCTGGGCGGTCTGGGTGTTGGCGGTCTGGGTGTAC 1347  
|||||  
118 uValGlyAlaAlaGlyLeuGlyGlyLeuGlyValGlyGlyLeuGlyValP 134  
1348 CGGGCGTTGGTGGTCTGGGTGGCATCCCGCCGGCGGCGGCAGCTAAAGCG 1397  
|||||  
135 roGlyValGlyGlyLeuGlyGlyIleProProAlaAlaAlaAlaLysAla 150  
1398 GCTAAATACGGTGCAGCAGGTCTGGGTGGCGTTCTGGGTGGTGGTGTCA 1447  
|||||  
151 AlaLysTyrGlyAlaAlaGlyLeuGlyGlyValLeuGlyGlyAlaGlyGl 167  
1448 GTTCCCACTGGGCGGTGTAGCGGCACGTCCGGGTTTCGGTCTGTCCCCGA 1497  
|||||  
168 nPheProLeuGlyGlyValAlaAlaArgProGlyPheGlyLeuSerProI 184  
1498 TCCTCCCAAGCGGTGCATGCCTGGGTAAAGCTTGCGGCCGTAAACGTAAA 1547  
|||||  
185 lePheProGlyGlyAlaCysLeuGlyLysAlaCysGlyArgLysArgLys 200

Figure 8(2)



# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/AU 98/00564

## A. CLASSIFICATION OF SUBJECT MATTER

Int Cl<sup>6</sup>: C07K 14/435, C07H 21/04, A61K 38/17, C12N 15/12, C12P 21/02

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC C07K 14/435, C07H 21/04, A61K 38/17, C12N 15/12, C12P 21/02

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
ANGIS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Proc. Natl. Acad. Sci. USA, Volume 84, issued August 1987, Z. Indik et al, "Alternative splicing of human elastin in RNA indicated by sequence analysis of cloned genomic and complementary DNA", pages 5680 to 5684 whole document	1-47, 50-65
X	Connective Tissue Research, Vol. 16, issued 1987, Z. Indik et al, "Structure of the 3' region of the human elastin gene : Great abundance of Alu Repetitive sequences and few coding sequences", pages 197 to 211 whole document	1-47, 50-65

☒ Further documents are listed in the continuation of Box C

☐ See patent family annex

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"&" document member of the same patent family

Date of the actual completion of the international search  
16 October 1998

Date of mailing of the international search report  
22 OCT 1998

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# INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU 98/00564

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Cell, Vol. 86, issued July 12 1996, J.M. Frangiskakis et al, "LIM-kinase 1 Hemizyosity Implicated in Impaired Visuospatial Constructive Cognition", pages 59 to 69 whole document	1-13, 18-29, 42-47, 50-62
X	Laboratory Investigation, Vol. 58, No. 3, issued 1988, M.J. Fazio et al, "Isolation and Characterization of Human Elastin cDNAs, and Age-Associated Variation in Elastin Gene Expression in Cultured Skin Fibroblasts", pages 270 to 277 whole document	1-13, 18-29, 38-47, 50-62
X	The Journal of Investigative Dermatology, Vol. 91, No. 5, issued November 1988, M.J. Fazio et al. "Cloning of Full-length Elastin cDNAs from a Human Skin Fibroblast Recombinant cDNA Library : Further Elucidation of Alternative Splicing Utilizing Exon-specific Oligonucleotides, pages 458 to 464 whole document	1-13, 18-29, 42-47, 50-62
X	Genomics, Vol. 36, issued 1996, L.R. Osborne et al, "Identification of Genes from a 500 kb Region at 7q11.23. That is commonly deleted in Williams Syndrome Patients", pages 328 to 336. whole document	1-5, 18-29, 42-47, 50-62
X	The Journal of Biological Chemistry, Vol. 264, issued May 25 1989, M.M Bashir et al, "Characterization of the Complete Human Elastin Gene", pages 8887 to 8891 whole document	1-5, 10-13, 42-47, 50-62